NATIONAL MARROW DONOR PROGRAM®

Entrusted to operate the C.W. Bill Young Cell Transplantation Program,
including Be The Match Registry®

July 26, 2012

CDR Sheri Parker
Office of Naval Research (ONR 342)
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: Final Report of the National Marrow Donor Program®

Reference: Grant #N00014-08-1-0058 between the Office of Naval Research and the National Marrow Donor Program

Dear CDR. Parker:

In accordance with the requirements of the Referenced Cooperative Agreement, the enclosed subject document is provided as the Final Report for each statement of work task item of the Grant for the period of November 01, 2007 through October 30, 2009.

With this submittal of the Final Report, the National Marrow Donor Program has satisfied the all reporting requirements of the above referenced Grant.

Should you have any questions as to the scientific content of the tasks and the performance activity of this progress report, you may contact our Chief Medical Officer – Dennis Confer, MD directly at 612-362-3425.

Please direct any questions pertaining to the Grant to my attention (612-362-3403 or at cabler@nmdp.org).

Sincerely,

Carla Abler-Erickson

Carla Abler-Erickson, M.A.
Contracts Manager

Enclosure: One (1) copy of subject document

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14. ABSTRACT

1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors : Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation**:** Create a platform that facilitates multicenter collaboration and data management.

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Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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National Marrow Donor Program® N00014-08-1-0058

Development of Medical Technology for Contingency Response To Marrow Toxic Agents

FINAL REPORT

November 01, 2007 – October 30, 2009

National Marrow Donor Program® N00014-08-1-0058
HLA Typing for Bone Marrow Transplantation
FINAL REPORT
November 1, 2007 – September 30, 2009

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ACRONYM LIST

AABB	American Association of Blood Banks
AFA	African American or Black
AML	Acute Myelogenous Leukemia
API	Asian Pacific Islander
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)
ASBMT	American Society for Blood and Marrow Transplantation
ASH	American Society of Hematology
ASHI	American Society for Histocompatibility and Immunogenetics
ASPR-HHS	Assistant Secretary of Preparedness and Response, Department of Health and Human Services
AUC	Area Under the Curve
B-LCL	B-Lymphoblastoid Cell Lines
BMDW	Bone Marrow Donors Worldwide
BMT	Bone Marrow Transplantation
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network
BRT	Basic Radiation Training
CAU	Caucasian
CBB	Cord Blood Bank
CBU	Cord Blood Unit
CDC	Centers for Disease Control
CHTC	Certified Hematopoeitic Transplant Coordinator
CIBMTR	Center for International Blood & Marrow Transplant Research
CIMS	Crisis Information Management System
CME	Continuing Medical Education
CSRS	Critical Staff Recovery Site
CSS	Custom Search Support
CT	Confirmatory Testing
DC	Donor Center
DIY	Do it yourself
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
D/R	Donor/Recipient
EBMT	European Group for Blood and Marrow Transplantation
EM	Expectation Maximization
FDA	Food and Drug Administration
FMHQ	Family Medical History Questionnaire
Fst	Fixation Index
GETS	Government Emergency Telecommunications Service
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)
GvHD	Graft vs Host Disease

ACRONYM LIST (continued)

HCT	Hematopoietic Cell Transplant
HHS	Health and Human Services
HIS	Hispanic
HLA	Human Leukocyte Antigen
HML	Histoimmunogenetics Mark-up Language
HPS	Health Physics Society
HR	High Resolution
HRSA	Health Resources and Services Administration
HSC	Hematopoietic Stem Cell
HW	Hardy Weinberg
IBWC	Immunobiology Working Committee
IDM	Infectious Disease Markers
IHWG	International Histocompatibility Working Group
IPR	Immunobiology Project Results
IRB	Institutional Review Board
IS	Information Services
IT	Information Technology
KIR	Killer Immunoglobulin-like Receptor
MHC	Major Histocompatibility Complex
MOU	Memorandum of Understanding
MRQ	Maternal Risk Questionnaire
MTE	marrow toxic event
NAM	Native American Indian/Alaskan Native
NCBI	National Cord Blood Inventory
NIH	National Institutes of Health
NIMS	National Incident Management System
NK	Natural Killer
NMDP	National Marrow Donor Program
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
QC	Quality control
RBC	Red Blood Cell
RCC	Renal Cell Carcinoma
RCI-BMT	Resource for Clinical Investigations in blood and marrow transplantation
REAC/TS	Radiation Emergency Assistance Center/Training Site
REMM	Radiation Event Medical Management
RFQ	Request for Quotation
RITN	Radiation Injury Treatment Network
ROC	Receiver Operator Characteristics
SAN	Storage Area Network

ACRONYM LIST (continued)

SBT	Sequence Based Typing
SCTOD	Stem Cell Therapeutics Outcome Database
SNS	Strategic National Stockpile
SOP	Standard Operating Procedure
SSA	Search Strategy Advice
SSOP	Sequence Specific Oligonucleotide Probes
SSP	Sequence Specific Primers
STAR®	Search, Tracking and Registry
TC	Transplant Center
TSP	Telecommunications Service Priority
WebEOC	Web Emergency Operations Center
XML	eXtensible Mark-up Language
TNC	Total Nucleated Cell
TOPOFF4	Top Officials 4 a Federal Exercise
URD	Unrelated Donor
WU	Work-up

Executive Summary

In 1986, Congress appropriated funds to begin development of the National Bone Marrow Donor Registry. Today, 23 years later, the National Marrow Donor Program (NMDP), as the contractor for the Registry, has built a racially diverse donor registry of nearly 8 million donors, facilitated more than 33,000 hematopoietic stem cell transplants, developed comprehensive research programs to improve post-transplant outcomes and established a network of transplant centers (TCs) capable of treating casualties resulting from military or terrorist actions, as well as patients suffering from leukemia, aplastic anemia and other life-threatening diseases.

Contingency Preparedness Planning

During this funding period, multiple projects were accomplished to further expand and develop the Radiation Injury Treatment Network ™ (RITN). Multiple physician and Network staff education seminars and training sessions were conducted including a conference attended by over 90 professionals. RITN centers were identified as a response asset for both the Republican National Convention and the Democratic National Convention in the event of a mass casualty incident resulting in marrow toxic injuries. Existing relationships were fortified and new relationships were forged with federal agencies for contingency response.

The NMDP's Operational Continuity Plan was finalized and approved by the CEO to ensure continuation of essential operations during a catastrophic disaster affecting the headquarters. Essential communication assets necessary for the NMDP's emergency operations were updated and periodically tested to ensure ongoing availability when needed.

NMDP Information Technology (IT) department completed several upgrades and enhancements to the NMDP information and communication structures. These upgrades and enhancements include projects such as Full Disaster Recovery Testing for Tier 1, 2, and 3 applications, Development of the Donor Contingency Portal to improve response processes for selectively identified donors, Cord Blood Bank inventory additions, Cord Blood Bank operational services (Electronic Query submission, CL Query output selection, product recovery data collection, updated HLA automated notification), Repository operational services (storing new samples, simplification of repository workflow), Regulatory Requirements (CMS Lab certification, Addition of ID to OCR form, Donor IDM updates), Operational efficiencies (Electronic Workup enhancements, HML message enhancements, Sample Storage improvements), Donor Center operational services and recruitment support (Search screen redesign, New Donor Notes, HHQ enhancements, Site Maintenance redesign, Communications History, DIY).

Rapid Identification of Matched Donors

Published research data have clearly defined the relationship between HLA matching and optimal patient outcomes following unrelated adult donor transplantation. Continually working to increase the genetic diversity of the Registry helps to ensure that more patients will be able to locate a suitably matched stem cell product for a transplant**.** During this time frame, NMDP donor centers (including Department of Defense (DoD)) and recruitment groups added 374,840 minority race and 407,588 Caucasian adult donor volunteers. All were typed for HLA-A, B and DRB1. Navy funding supported the typing of 118,134 of these culturally diverse new donors.

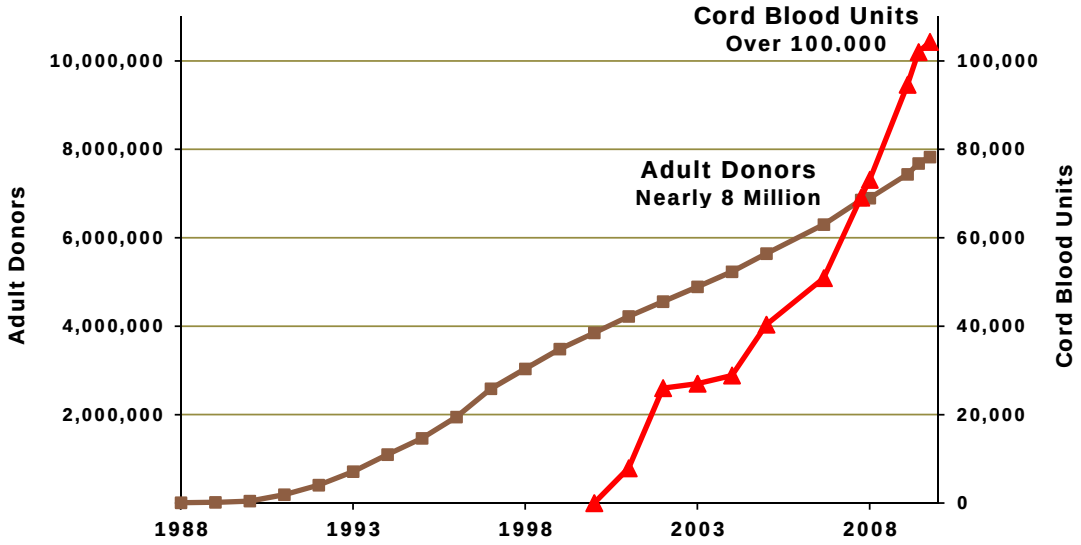
Advancing technology improved performance and pricing
Continued advances in laboratory methods and supporting equipment have positively impacted the level of typing resolution for newly recruited volunteer donors. As of September 2009:

- 84% of new donors received higher than intermediate HLA-A, B typing
- 34% of new donors received intermediate HLA-C typing
- 100% of new donors received higher than intermediate HLA- DRB1 typing

The cost of HLA typing for new volunteer donors decreased by 12.1% between **2007 and 2008.**

The NMDP's exacting quality control processes have successfully increased the quality of typing received through the contract laboratory network. The effectiveness of this program and the efforts of a highly qualified high-volume HLA typing laboratory network has resulted in a combined HLA class I and class II QC accuracy rate for this period of 99.91%.

Registry Growth: Adult Donors and Cord Blood Units



Five HLA typing projects were completed in this contract which improved the HLA typing quality of listed adult volunteers and allows for improved speed of donor selection for patients with these alleles, including non-Caucasian patient searches. These projects highlight the importance of technical oversight of the Registry data.

Expert HLA advisors contributed involvement in supplying free search strategy advice to 114 different transplant centers and included 1593 reviews. These experts were an integral part of the continued validation of HapLogic in the Traxis application and have contributed ideas for the future design planning additional enhancements to the HapLogic algorithm.

Educational resources to improve appropriate application of transplant and increase evidence-based decision-making were developed and disseminated. Results of initial programs were measured, and revisions to enhance value and participation were implemented.

Immunogenetic Research

The high resolution HLA typing of paired donor and recipient samples continued to provide substantive data to increase the understanding of the impact of HLA matching on patient outcome. The project data were also used to assess genetic diversity within the NMDP transplant population and Registry and fed into the HapLogic matching algorithm. Data generated through the project are utilized in all unrelated donor research studies conducted through the Center for International Blood and Marrow Transplant Research (CIBMTR). Testing was completed on an additional 1,047 donor/recipient and 126 cord/recipient pairs during the project period, bringing the total enrolled to over 14,000.

HLA genes other than those characterized in the Donor/Recipient Pair Project and non-HLA genetic factors may all influence the suitability and success of allogeneic stem cell transplants. To further elucidate the impact on matching, another important research study funded by this grant investigated the allelic diversity of the Killer Immunoglobulin-like Receptor (KIR) ligands. During the previous period, the KIR Typing Pilot Project completed the final typing on 435 Caucasian donor samples for 14 KIR genes (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1). However, the study encountered a high degree of genetic polymorphism and allelic ambiguity in the KIR loci. During this period all 91 remaining discrepancies were resolved and 128 potential new KIR alleles were re-analyzed. Seventy-eight samples were re-typed with 46 novel alleles described and submitted to the WHO nomenclature committee for registration and naming.

During this grant period, NMDP continued development of the IPR (Immunobiology Project Results) database and application. This database will replace the existing HLA donor/recipient pairs database and has the capacity to process KIR, SNPs, or any other Immunobiological tests. Input file (HML) processing has been developed and the analysis of processing rules (lab-to-lab comparison, ambiguity analysis, data audits) is nearing completion.

Funding supported activities to optimize the operations of the NMDP Research Sample Repository. Informational tools were enhanced to manage and monitor the inventory. A pilot projects was conducted to evaluate the use of whole genome amplification (WGA) technology as a method to expand low inventory donor, cord blood and recipient research samples. The project was successfully completed and the WGA procedure will be operationalized in the next year.

Clinical Research in Transplantation

Improving strategies to avoid and manage graft-versus-host disease (GVHD) is an essential step in improving the outcomes of transplantation and, consequently, the ability to incorporate transplantation as an effective therapy in a variety of settings including contingency situations. The goal of the research activities funded through this grant has been to increase the understanding of the immunologic factors important in HCT.

During this grant, activities within the Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT) continued. The goal of this program is to provide an avenue for investigators to obtain statistical and data management support for Phase I and II prospective trials focusing on addressing various transplant issues. The following key elements were completed:

- Clinical Trials Advisory Committee (CTAC) met for its annual in person meeting during this grant period. This meeting occurred at the 2008 Tandem meetings. This committee has been charged with providing scientific review and recommendations on clinical trial proposals. The committee reviewed a total of 5 proposals of which two were approved to move forward to protocol developments and three denied. One of the approved proposals did not move to protocol development due to PI decision to not move forward with the study at this time.
- Managed all elements of the Adult Double Cord in patients with hematologic malignancies trial. Staff opened remaining sites, managed accrual and performed site monitoring. At the end of this grant year, a total of 16 patients were accrued on this trial.
- Staff continued to provide support to the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) PBSC vs Marrow Phase III trial. This support included managing the donor component of the study but also assisting the BMT CTN in the area of accrual initiatives on the recipient portion of the study. Activities included were:
    - Supported Donor Centers by providing continued training, tools and updates
    - Performed monitoring activities at the Donor Centers
    - 328 donor/recipient pairs enrolled during this grant period.
- During this grant period, database development was completed for the Lenalidomide after allogeneic HCT for Myeloma trial. The trial was activated and accrual began. During

this time, defects were identified and staff worked with the trial management system vendor to correct.

Support of the Observational Research program included statistical hours for managing studies within the Immunobiology, GVHD, and Graft Sources Working Committees. During this grant period staff performed proposal review, protocol development, data preparation, data analysis, and manuscript preparations. Details regarding the Immunobiology activities can be found in IID1.3 below. The GVHD and Graft Sources Working Committees published 4 manuscripts. During the grant period staff performed various other functions on over 20 other studies.

During the grant period, the NMDP Cord Research Subcommittee met monthly via conference call to plan activities. The group monitored the NMDP cord blood proficiency testing program and evaluated several protocol modifications in an attempt to minimize interlab testing variability. The subcommittee participated in the submission of a grant application to evaluate cord blood potency assays and initiated preparations of a white paper describing best practices for cord blood assay assessment. The subcommittee also developed two educational sessions for the NMDP Council meeting.

To further stimulate completion of immunobiology studies within the CIBMTR, grant funds were used to provide monetary support to investigators whose studies require modest supplemental funding for completion. Three of these grants were awarded during the grant period. Grant funds also supported significant outreach efforts by the IBWC leadership to increase exposure for the IBWC to basic scientists. In addition, the IBWC continued work on the 36 active studies in the committee, accepted seven new proposals for analysis, presented eight abstracts and submitted seven studies for publication.

END – EXECUTIVE SUMMARY

II.A. Contingency Preparedness – Hypothesis 1:

Recovery of casualties with significant myelosuppression following radiation or chemical exposure will be optimal when care plans are designed and implemented by transplant physicians

Aim A.1.1: Secure Interest of Transplant Physicians

In working to accomplish this Aim, the NMDP focused on the education of transplant physicians and their staff and the inclusion of a subset of physicians in the development of the Radiation Injury Treatment Network ™ (RITN).

A critical piece of the research program was to provide investigators with information on the underlying biology and medicine of radiation. During the performance period RITN centers were encouraged to train staff using the NMDP Basic Radiation Training (BRT) course which provided physicians and their staff the opportunity to gain a basic understanding of radiation. The BRT course contains four sections and a 29 question exam that is submitted via the Internet. At the completion of this performance period, a total of 1,997 people had successfully completed this training; 895 during the 2008 fiscal year and 320 during the 2009 fiscal year.

As the number of RITN center staff who hadn't completed the Basic Radiation Training decreased and the percentage of RITN transplant centers that had conducted Grand Rounds presentations to their medical staff increased, a new means of education may be necessary.

As an interim solution to developing new self directed training, NMDP held an educational conference and sent RITN center staff to the Radiation Emergency Assistance Center and Training Site (REAC/TS) in Oak Ridge, TN on alternating years.

During this performance period a RITN educational seminar was held in Bethesda, Maryland, on May 18, 2009. This seminar, titled "Nuclear Terrorism: Hematology/Oncology Center Preparedness" drew 92 attendees. Attendees were solicited through the membership lists of ASBMT, ASH, Health Physics Society (HPS), as well as physicians from the NMDP Network. Physicians could earn seven (7) CME credits through the Medical College of Wisconsin.

The final seminar agenda consisted of an opening keynote address by RADM Anne Kneble (Deputy Director for Preparedness Planning in the Office of the Assistant Secretary for Preparedness and Response, United States Department of Health and Human Services)

- Morning group sessions included:
  - Threat Scenario Overview
  - National Disaster Medical System
  - Medical response expectations 10, 100, 1,000 miles from epicenter
  - Altered Standards of Medical Care Overview

    - NMDP Planning and data collection
- Afternoon interactive breakout workgroups included (each session was held three times so attendees could attend all sessions):
    - Altered Standards of Care
    - Logistical issues – bed mgmt, use of non-hospital locations, & staffing issues
    - Provision of medical care – early and late care
    - The conference culminated with a report of findings by the afternoon session moderators

The summary of findings presented many questions that need to be answered by all attendees once back at their institution:

- Altered Standards of Care findings:
    - Are there connections to institutions in our region for supplies, standards, policy and other obligations?
    - Who determines what the standards of care are?
    - Where are the gaps in care? Outpatient-inpatient connections, laboratory, and blood bank.
    - How can RITN become a regional resource?
- Logistical Issues findings:
    - Need to involve hospital administration to affect change.
    - Need to connect with burn centers.
    - Need formal connection to Strategic National Stockpile (SNS) for medications.
    - What is the licensure and liability of retired medical staff "activated" to help?
    - Can the NMDP help with related typing?
- Provision of Medical Care findings:
    - How do you surge to respond for: drugs, blood, beds, and staff?
    - Need to establish SOPs for outpatient care.
    - Does there need to be standards? What is worth delaying? Does there need to be a slightly larger inventory to bridge the gap of just in time inventory and what is needed for mass casualty?
    - How is this institutionalized into the hospital management plan, incident response plan, and with regional response plans?
    - How do you make local response agencies activate to respond to a national disaster?

The Advanced Radiation Medical Emergency training course conducted at REAC/TS is a course specially designed for RITN centers. It takes into account the knowledge of RITN center staff to optimize their time spent at training. Course lessons included:

- Basic Health Physics & Radiation Protection: Part I
- A History of Serious Radiological Incidents: The Real Risk
- Health Physics & Contamination Control: Part II
- Radiation Detection, Monitoring & Protection Laboratory Exercise & Quiz

- Diagnosis & Management of the Acute Radiation Syndrome (ARS)
- Diagnosis & Management of Internal Contamination
- Diagnosis & Management of Acute Local Radiation Injury & Case Review: Yanango Peru
- Radiation Sources & Radiological Terrorism
- Radiation Emergency Area Protocol Demonstration
- Radiation Emergency Medical Management Drill
- Radiation Dose Estimations – Problem Solving Session

Aim A.1.2: GCSF in Radiation Exposure

This Aim focused on non-transplant treatment guidelines and patient assessment related to the use of GCSF for patient treatment as a result of a marrow toxic mass casualty event such as radiation exposure.

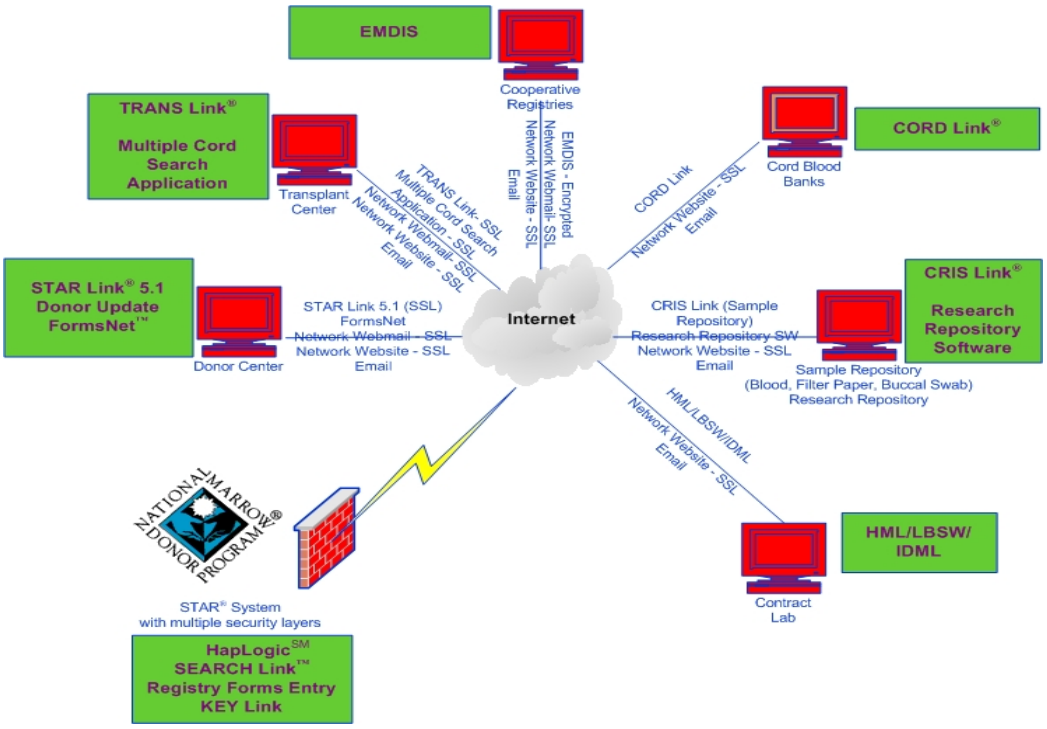
No activity was conducted during this period of performance related to this Aim.

Aim A.1.3: Patient Assessment Guidelines

Efforts related to this Aim focused on the development of transplant treatment guidelines and the associated support systems, including the refinement of guidelines for patient assessment and the operational and educational aspects of rapid product selection and transplant as necessary in a marrow toxic mass casualty event such as radiation exposure.

Figure 1 illustrates the Network application and communication infrastructures of the STAR System and Web-based ancillary systems; STAR Link, CORD Link, TRANS Link, Multiple Cord Search Application, CRIS Link (Repository software), and FormsNet. Along with SEARCH Link and the HapLogic matching algorithm (both of which are internal to NMDP), these systems provide rapid electronic communication and enable the NMDP to handle the high volume of transactions each day.

Figure 1: Network Center Communication



To help ensure that the NMDP systems would be fully capable of supporting the Network in the event of a radiation exposure, the following work was performed:

FormsNet

- FormsNet v2.6.1 and v2.6.2 were released including a number of bug fixes and enhancements including a major cleanup of forms tracking and internationalizations enhancements.

AGNIS

- AGNIS has been released to production for forms 2900 and 2450 (death form and pre-TED). The data curation effort to register all 11,000 data elements in the caDSR is making steady progress with collaboration with a number of curators at the Minneapolis and Milwaukee campuses of CIBMTR and NCI.

CORD Link

To support our quality efforts, the following changes were made to CORD Link Web:

- Electronic Query Submission - The Query Request Form is now submitted through the CORD Link application. The form is located on the side navigation menu under the Help menu. The Banks use this form to request query output that is not available through the CL Query Tool.
- CL Query Output Selection -The Output selection of the CL Query tool has been enhanced to be more user friendly and to include more fields available for output. The Output screen lets the user choose the query type. Standard produces a user selected output, and the NCBI option auto populates the fields needed or NCBI reporting.
- Product Recovery Form 2006 - The Form 680 was retired on Dec. 3, 2007. Data that have been captured in the Form 680 are part of the Form 2006. The Form 2006 has been added to the Forms Received section of CORD Link. The notification and functionality in CORD Link will be the same as the Form 680.
- HLA Alerts -CORD Link users have the option to receive HLA Update Alerts, the cord blood bank coordinator, or designated staff member(s) receive electronic notification through email. The implementation of the HLA alerts feature delivers HLA upload updates to the cord blood bank staff without requiring individuals to manually log into the application and check for new requests.
- A new action item was added to Workflow Management screen for the SCTOD (Stem Cell Therapeutic Outcomes Data) Data Form. The information will be passed to the CIBMTR for outcomes research.
- CORD Link users now have the option to subscribe to Alerts in the CORD Link Application.
  Users simply add an email address under their user profile to request desired alerts notification for search activity.
- The NMDP plans to replace Local ID with the recently implemented Full Local ID for all CBBs. Full ID Lookup will allow CBBs that are using the Full ID field to look up CBUs using their full ID. The Full Local ID eliminates the need for CBBs to truncate their ID numbers to fit into the ID field.
- Per FDA regulations, CORD Link was modified to include CMS laboratory certification status on the (Infectious Disease Marker) IDM questionnaire. The question is to be answered for all IDMs.
- Added “Bank did not test” option. Previously, the cord blood banks could not complete the form if they did not perform the test.
    - If the CBB does not have results captured for a particular test, checking the “Bank did not test” option will satisfy the field entry.
    - For cords that are shipped outside of the NMDP, and the Shipped to Other (SO) status is selected, entry of the Proposed Infusion Date, Transplant Center, and Recipient ID in the SCTOD form is now permitted.

To meet a regulatory requirement and increase product safety the following features were added:

- Cord Blood Banks can send OCR forms that are scanned or hand entered by the NMDP. The data are populated into the CORD Link application. For scanned forms, a PDF is available in CORD Link. The scanned forms, when printed, now contain an ID number at the bottom of each page thus eliminating the risk of loss in chain-of-custody by linking the information to the cord blood unit.
- All import tools were modified to include the CMS question which is now required due to FDA regulations.
- To increase cord blood bank efficiencies and allow users to quickly access and respond to important search information on a CBU, Email alerts generated by CORD Link now include a direct link to the NMDP's connect page at "connect.nmdp.org".

Cord Blood Bank Conversions completed:

- Sheba Bank 193 - Sheba went live with 1349 units. All units have been validated by both NMDP Business Analysts and CBB staff.
- Gift Of Life Bank 179 - GOL went live with 244 units. All units have been validated by both NMDP Business Analysts and CBB staff.

Research Sample Repository

The research repository software was upgraded with the following changes:

- Enabling the repository staff to store new samples types (amplified DNA, RNA and serum)
- Changing processing protocols to simplify repository workflow
- Reworked handling of related repository samples
- Re-factored sample note processing and storage
- Re-factored default vial calculations
- Refined duplicate recipient processing rules. The software was successfully deployed at the repository, and is in usage by the repository staff

STAR Link

The following features were added to STAR Link:

- Search Screen Redesign – non-workup search requests
- Site Maintenance Redesign – Phase 1
- Kit Requests – add Assigned-to
- Updates feature
- New Donor Notes – works with Search notes
- New Security Permissions: Center Support Services, Recruitment, Help Desk
- Added "Willingness to Consider" field
- Added new Kit Request ship to location: Employer Address
- Added new "All" quick link from Work Flow Management Screen
- Site Maintenance: Add Filters and Export
- Health History Questionnaire: Electronic STAR Link version

- E-mail link for Drive Detail Report
- SL Query: Add query selector to handle merged centers
- Tracking Sheet changes: Remove Short version & add Long version with Notes
- Drive Screen, Recruiter field: Remove "Recruiter not Shown" option
- Communications History - A new section has been created in STAR Link that shows automated communication.

Navy Contingency efforts in STAR Link Web and Do It Yourself (DIY)

This project enables the ability to electronically contact the donors via email and allow them to update their contact information and complete an online Health History Questionnaire (HHQ) from the DIY online platform. Information provided by the donor is securely transferred to the donor's record in STAR Link facilitating reporting, storage and review of this information in established donor management systems.

In 2009 new versions of the STARLink Web and Do It Yourself Donor (DIY) applications were developed.

Key features included were:

- HHQ – An electronic version of the entry of The DR/Prelim HHQ in STAR Link Web.
- Initiation of Online HHQ
- Ability of the HHQ to be completed online by the donor based on an email trigger sent to donors
- Ability for donor to review and update key contact information online to auto populate STAR Link record
- Review and verification of online HHQs
- Void of electronic HHQs to preserve integrity of stored documentation
- Reports that display original responses from donor that have completed an online HHQ and the status of all HHQs

Deployment Strategy included:

- Conducting a **Pilot** for the Online HHQ
    - Timeline was from 11/1 – 11/30.
    - Included the NMDP Call Back Unit and 3 Donor Centers
    - It was very successful from a user acceptance and overall metrics measurement perspective.
- Conducting a final **Rollout** of the Online HHQ application
    - Completed on 11/30
    - Included all Domestic NMDP Network Donor Centers, with the exception of the DoD and DKMS Americas.
    - Overall feedback and processing times continue to be monitored.

Project outcomes captured to date indicate:

- **Donors are responsive to online tools.** Between 10/1/09 – 12/31/09, new Online HHQ functionality resulted in:
    - 701 **"Completed"** HHQs
    - 194 "**in process"** HHQs

- **Donors report a high level of satisfaction with online tools.**
    - Approximately 40% of donors have given feedback through the email survey process
    - 94% of donors that were able to complete the HHQ online
    - Donors rated the following as 'excellent'
        - 94% for Easy to Understand
        - 91% for Convenient
        - 82% for Visual Appeal Appearance
- **Online tools introduce great efficiency to key donor screening functions.** Average time to process a HHQ was reduced from 27 to 13.5 minutes resulting in a 50% **reduction** in processing time per Online HHQ.

Given the high acceptance rate for this functionality along with the gains to productivity of donors screened using this method, it is expected that NMDP will gain:

- The capability to double the capacity to process an HHQ using the same number of staff resources.
- The ability to scale for a contingency event requiring confirmation of the availability and suitability of a large number of donors.

Other efforts for the Contingency Project in the 4th Quarter of 2009 included the following in process items:

- Detailed project and budget plan for Event Portal (Preliminary Search) Release – scheduled for late 1st Qtr 2010.
- Initial review of the Event Portal Screen functionality.
- Identification of an Enterprise Architecture approach for the Import Process for Preliminary Search.

Project Management and Quality Assurance Components which will be used to manage the next Release

Aim A.1.4: National Data Collection Model

The focus of this AIM was to define and develop a national data collection and management model to collect data resulting from a mass radiological exposure event.

During this period the protocol to collect data connected to a mass casualty event resulting in marrow toxic injuries was maintained through the CIBMTR Institutional Review Board (IRB)

review and approval process. Links to updated copies of these documents are available on the RITN website.

Of note, this protocol is incorporated into the standard NMDP data collection process used by all NMDP transplant centers ensuring that the form is utilized at each institution and therefore available during a contingency incident. These protocols and form will be reviewed annually by participating NMDP IRBs and therefore will be in place and ready for any event resulting in marrow toxicity.

During this period of performance the RITN Executive Committee produced a publication and a response to comments made by pre-eminent European physicians preparing for a radiological disaster.[1,2] This publication and the discussion of the United States vs. European perspective initiated cross Atlantic discussions that culminated with a meeting of the EBMT Nuclear Accident Committee and the RITN Executive Committee in Ulm, Germany on June 30 and July 1st, 2008. Standardization of data collection elements between the United States and Europe was discussed; this would simplify the response to and future research related to a radioactive disaster with mass casualties resulting in marrow toxic injuries. Attendees of the meeting included representatives from four countries; all considered subject matter experts in treatment of marrow toxic injuries; attendees included:

- Judith Bader, MD — United States
  Department of Health and Human Services, Washington, D.C.
- Axel Böttger, MD — Germany
  Federal Ministry of Environment,
  Nature Protection and nuclear Safety, Bonn
- Cullen Case, CEM — United States
  National Marrow Donor Program, MN
- Nelson Chao, MD — United States
  Duke University, Radiation Countermeasures Center of
  Research Excellence, NC
- John Chute, MD — United States
  Duke University, NC
- Norman Coleman, MD — United States
  Department of Health and Human Services, Washington, D.C.
- Dennis Confer, MD — United States
  National Marrow Donor Program, MN
- Theodor M. Fliedner, MD — Germany
  Radiation Medicine Research Group, Ulm University
- Arnold Ganser, MD — Germany
  Department of Hematology and Oncology,
  Medical University Hanover

- Patrick Gourmelon, MD — France
  Institut de radioprotection et de sûreté nucléaire,
  Fontenay-aux-Roses
- Dieter Graessle, Dipl.- Math. Oec. — Germany
  Radiation Medicine Research Group, Ulm University
- Juergen Griebel, MD — Germany
  Institute of Radiation Hygiene,
  Federal Office for Radiation Protection, Munich
- Robert Krawisz — United States
  American Society for Blood and Marrow Transplantation, IL
- Viktor Meineke, MD — Germany
  Bundeswehr Institute of Radiology, Munich
- Dietger Niederwieser, MD — Germany
  European Group for Blood and Marrow Transplantation and
  Department of Hematology and oncology, University of Leipzig
- Matthias Port, MD — Germany
  Department of Hematology and Oncology,
  Medical University Hanover
- Ray Powles, MD — United Kingdom
  Nuclear Accident Committee of EBMT, London
- Bhawna Sirohi, MD — United Kingdom
  Nuclear Accident Committee of EBMT, London
- David Weinstock, MD — United States
  Dana-Farber Cancer Institute, MA
- Albert Wiley, MD — United States
  Radiation Emergency Assistance Center/Training Site, TN
- Collette Steinwachs — Germany
  Radiation Medicine Research Group, Ulm University

As a result of this meeting the paper *Stem Cells, Multi-organ Failure in Radiation Emergency Medical Preparedness: A US/European Consultation Workshop* was published in Stem Cells to disseminate the key points that were agreed upon by both European and American experts.[3]

II.A. Contingency Preparedness – Hypothesis 2:

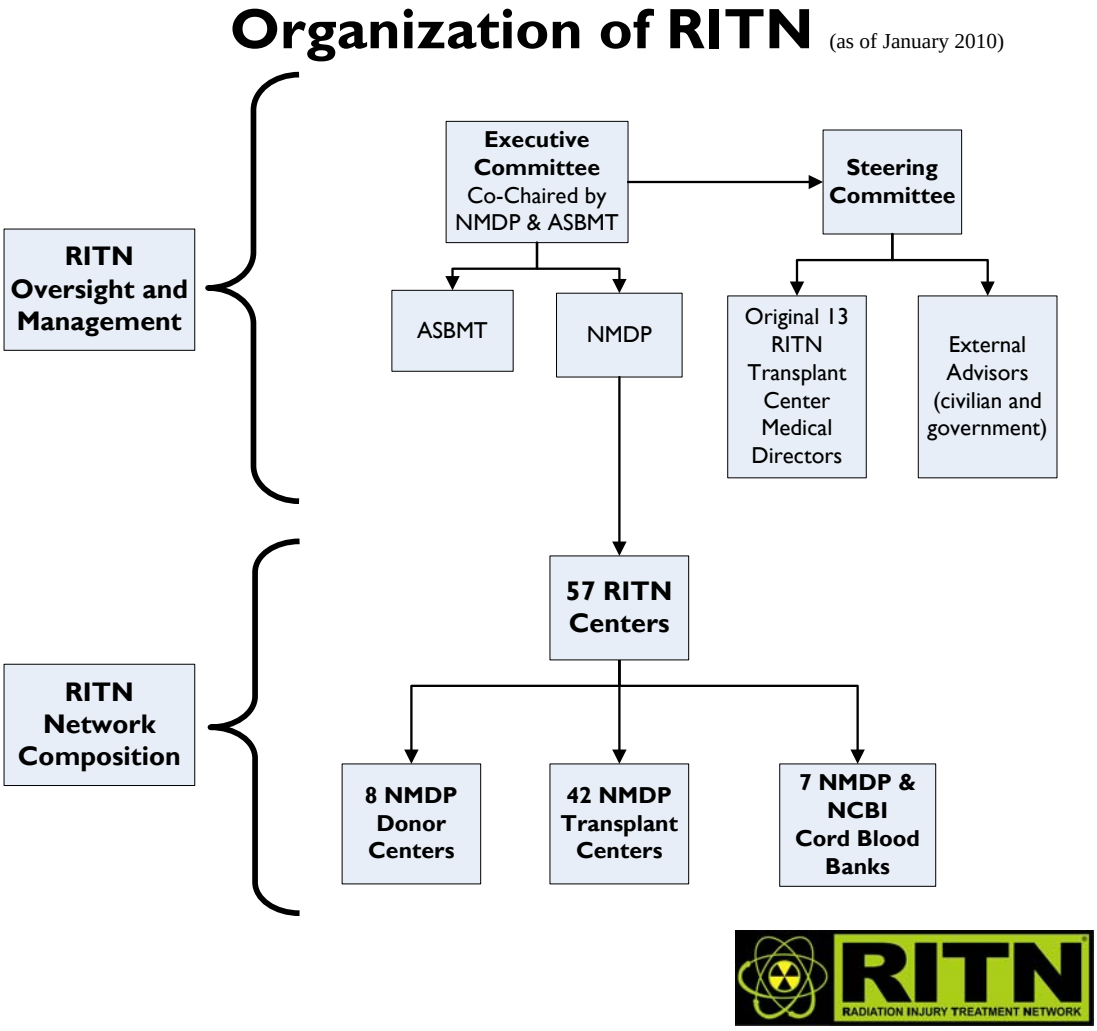
Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.

Aim A.2.1: Contingency Response Network

The RITN and its efforts were the focus of this Aim. The RITN was organized to provide comprehensive evaluation and treatment for victims of radiation exposure or other marrow toxic injuries. The RITN develops treatment guidelines, educates health care professionals, works to expand the network, and coordinates situation response. The RITN is a cooperative effort of the NMDP and The American Society for Blood and Marrow Transplantation (ASBMT).

RITN centers include transplant centers, donor centers, and cord blood banks. Partner organizations with clinical experts participate through the RITN Steering Committee (see Figure 2) with the medical directors (or their delegate) from the original 13 transplant centers. The RITN Steering Committee typically meets twice a year to discuss the further development of the RITN, its treatment procedures, training materials and other related products. An Executive Committee (comprised of NMDP, ASBMT representatives and technical advisors) meets periodically throughout the year by conference call.

Figure 2. Organization of RITN



The **RITN Steering Committee** consists of transplant physicians from the 13 original transplant centers (see Aim 2.1 for further details), experts in the field of transplantation, government and non-governmental partners. During the period of performance two (2) meetings of this group were held:

- February 2009
- May 2009

Outcomes of these meetings included:

- Review of maintaining the momentum of RITN over time

- Overview presentation about its activities from the Office of the Biomedical Advance Research and Development Authority (BARDA) from DHHS-ASPR
- Determination to work on establishing connections between RITN and burn centers

The **RITN Executive Committee** provides direction for RITN and accomplishes the bulk of work in preparing products developed in RITN's name pending input from the Steering Committee. The RITN Executive Committee is chaired by a representative from the NMDP and from the ASBMT. There are also other members and technical advisors that support the activities of this committee; as of September 30, 2009 committee composition consisted of:

- Chairs:
  - NMDP Chair: Dennis Confer, MD
  - ASBMT Chair: Alan Leahigh
- Committee Members:
  - Transplant Physician: Nelson Chao, MD
  - Transplant Physician: Daniel Weisdorf, MD
  - Transplant Physician: David Weinstock, MD
  - ASBMT Deputy: Robert Krawisz
  - RITN Program Manager: Cullen Case, CEM
- Advisors:
  - Technical Advisor: Richard Hatchett, MD
  - Technical Advisor: John Chute, MD

During this performance period the Executive Committee met by conference call periodically to review ongoing projects and develop products. Outcomes of these meetings include:

- Identification of possible bone marrow transplant programs to be invited to join RITN in FY09
- Development of the agenda and content of the 2009 RITN Conference ""Nuclear Terrorism: Hematology/Oncology Center Preparedness"
- Development of agendas for Steering Committee meetings
- Coordination of presentations by external subject matter experts at the Steering Committee meetings
- Coordination of partnerships with radiation emergency response organizations; including World Health Organization – Radiation Emergency Medical Preparedness and Assistance Network, and The European Group for Blood & Marrow Transplantation

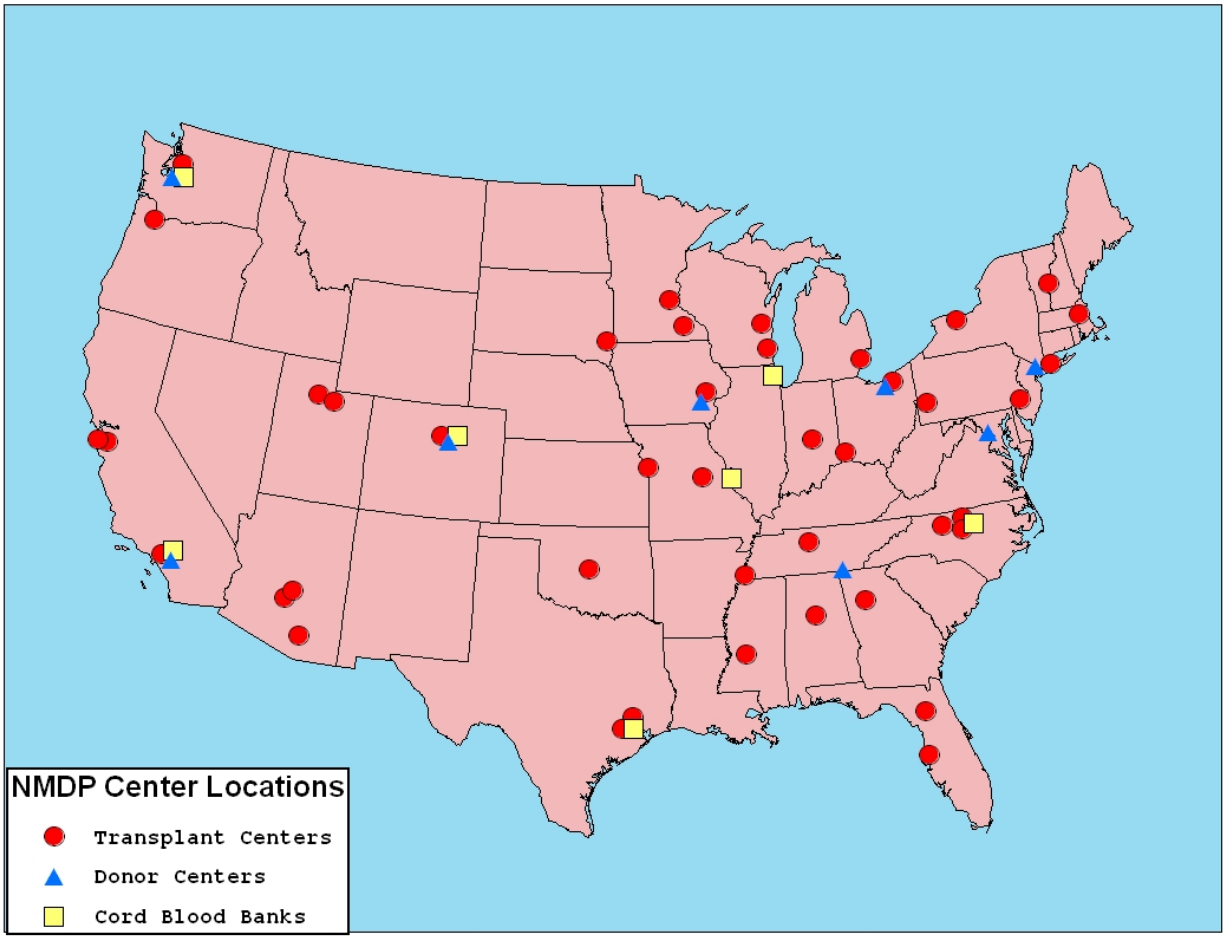
Participating RITN centers work to establish and test a documented process for the intensive supportive care for the treatment of radiation victims from a mass casualty incident resulting in marrow toxic injuries. To prepare for such an event, RITN centers develop, maintain and improve standard operating procedures of how their organization would respond to such an event. Some centers are selected to work on special projects; these projects have included

protocol development, education material development, presentation development, the GCSF Stockpile Assessment, and contingency related research opportunities where applicable.

RITN centers adopt, to the extent practical, the RITN standardized treatment guidelines, donor selection criteria, data collection plan, and other related documents developed by the RITN Executive and Steering Committees.

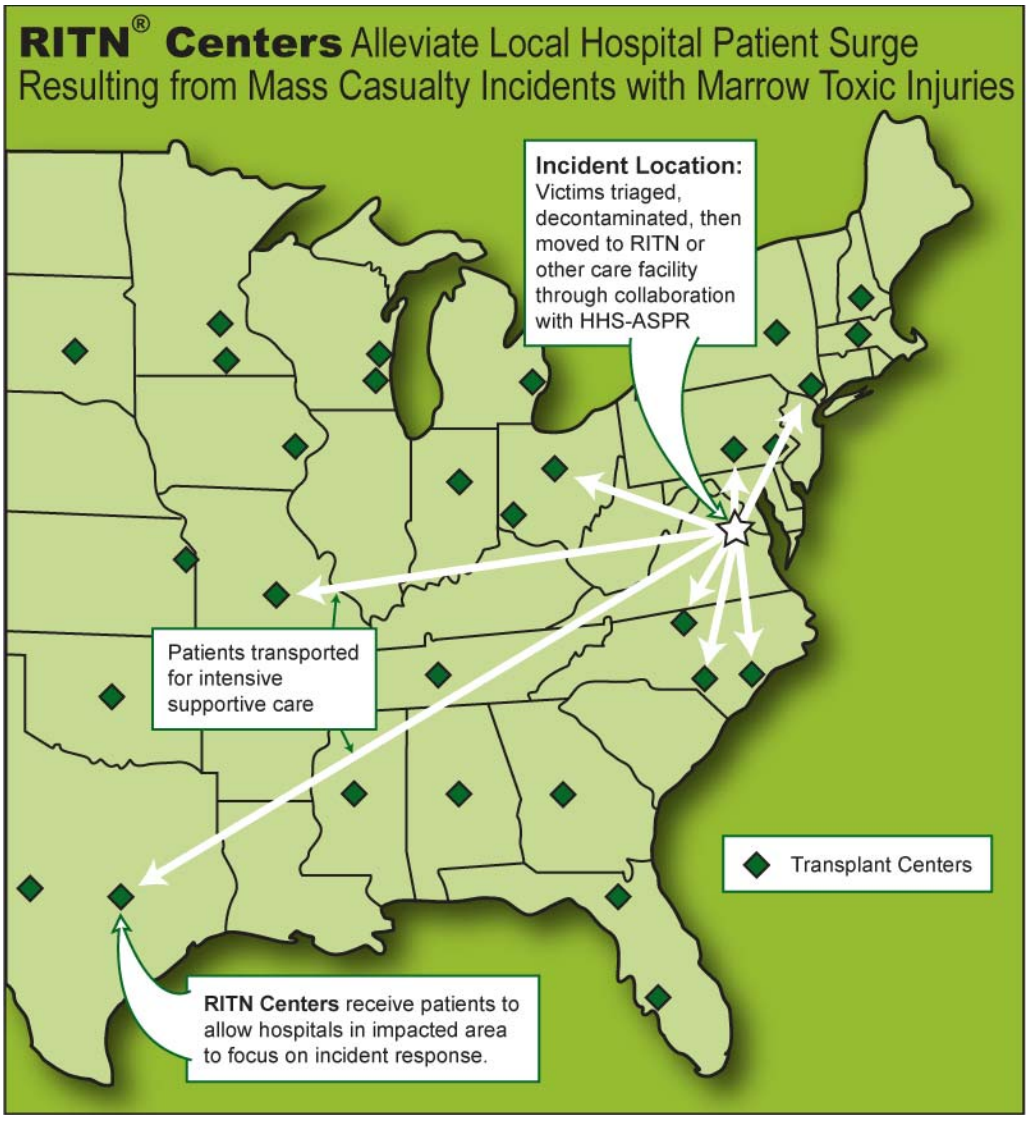
In developing the RITN, the NMDP began in 2005 with 13 transplant centers. These centers have grown to include 57 total participating centers distributed across the United States: 42 transplant centers, eight (8) donor centers, and seven (7) cord blood banks (see Figure 3 below for distribution across the United States). Each of these centers created standard operating procedures describing how their organization would respond to a mass casualty incident with marrow toxic injuries, participated in regular drills, an annual tabletop exercise, as well as educated their staff through the NMDP Basic Radiation Training or the RITN Grand Rounds presentation.

Figure 3. RITN Center Distribution by Type (as of January 2010)



It is very important to keep in mind that the RITN is not a first responder organization. All participating centers are preparing to respond to an event that occurs in another city or distant location from their area. The NMDP anticipates that the RITN will receive patients from another part of the country to alleviate their medical load and to provide the best care possible for the victims of a mass casualty incident resulting in marrow toxic injuries (see Figure 4 below).

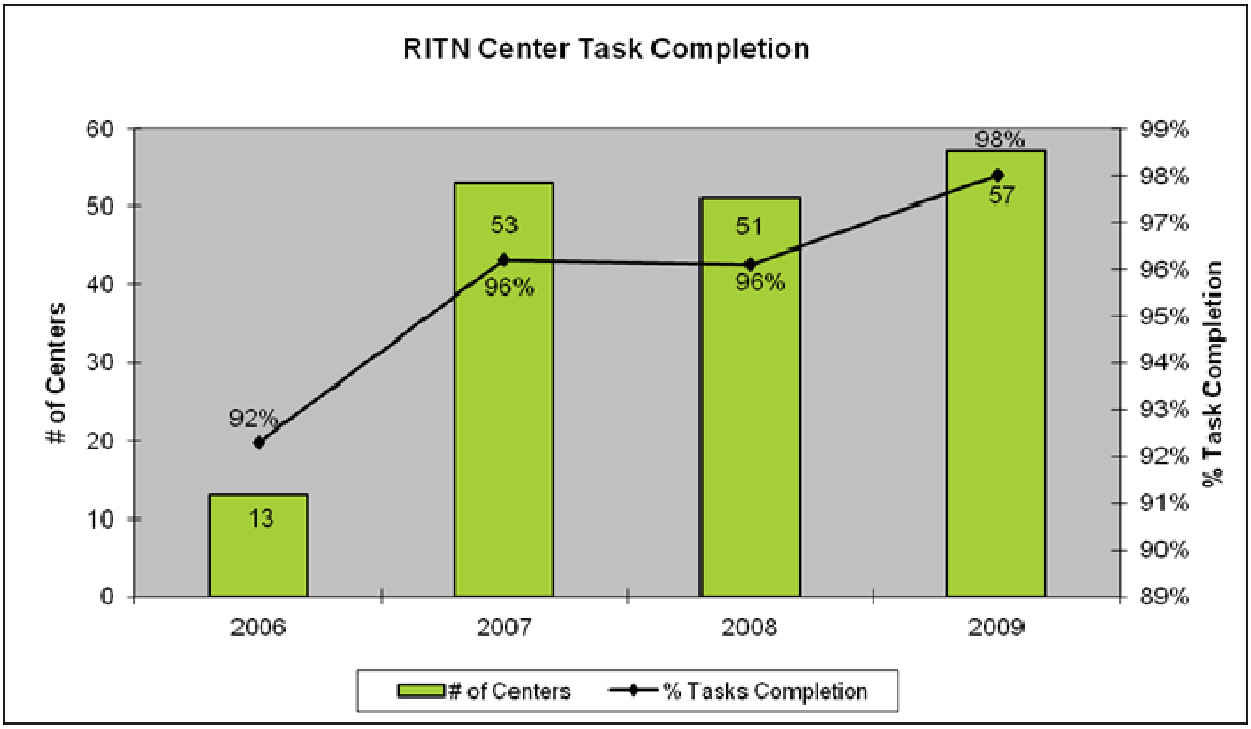
Figure 4. RITN center MTE response plan



To accomplish this RITN centers are required to complete tasks each year. For this grant the tasks were to: 1) update their RITN disaster SOP, 2) complete the RITN tabletop exercise, 3) train 20 new staff using the NMDP BRT, 4) either conduct a RITN Grand Rounds presentation or a RITN overview presentation to an appropriate contingency response group, and finally 5)

submit Capabilities Reports via Internet as requested. The RITN center task completion rate during this period of performance improved from 96% to 98% of tasks completed on schedule (Figure 5).

Figure 5. RITN Center Task Completion



The RITN would not be able to succeed in response to a mass casualty incident without the support of partner organizations. The NMDP has worked diligently to develop these relationships so that when an event occurs it will be already known who to call. Two levels of partnerships have been developed, formal and informal. Formal relationships are documented through a Memorandum of Understanding (MOU). The NMDP currently has an MOU with the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services (ASPR-HHS), the ASBMT, and the American Association of Blood Banks (AABB). Organizations that hold informal partnerships include:

- RADCCORE at Duke University
- NIH-NAIAD-DAIT
- NIH-NLM-REMM
- NCI
- WHO-REMPAN
- REAC/TS

To increase the visibility of RITN and make new connections with additional organizations and agencies, overview presentations were given to various professional groups and government agencies. During the project period, RITN made eleven presentations to a total of over 500 attendees. The groups receiving RITN presentations during this period of performance include:

- Indo-US Workshop on Medical Countermeasures for Radiation Injury: Current and Evolving Technologies in New Delhi India (Cullen Case, CEM)
- 18th Nuclear Medical Defense Conference in Munich Germany (Cullen Case, CEM)
- AABB annual meeting in Montreal Canada (Cullen Case, CEM)
- Office of the Biomedical Advance Research and Development Authority (BARDA) from DHHS-ASPR in Washington, D.C. (Nelson Chao, M.D.)
- Bio Dose 2008 in Dartmouth, NH (John Chute, M.D.)
- Advisory Council on Blood Stem Cell Transplantation in Washington, D.C. (Nelson Chao, M.D.)
- 12th Coordination and Planning meeting of the WHO-REMPAN Collaborating Centers and Liaison Institutions in Buenos-Aires, Argentina (David Weinstock, M.D.)
- AABB Disasters Task Force annual meeting (Raymond Hornung, CBCP)
- RITN poster was presented at the DHHS Integrated Medical, Public Health, Preparedness and Response Training Summit in Dallas, TX
- RITN poster was presented at the 55th Annual Health Physics Society Meeting in Minneapolis, MN

Aim A.2.2: Develop and test standard operating procedures, in conjunction with core transplant centers, to manage the activities required to HLA type siblings of casualties to evaluate their potential as HSC donors for their affected family member.

The focus of this Aim was to develop and test standard operating procedures that would manage the activities required to HLA type and evaluate transplant suitability of siblings of casualties.

During this period of performance multiple meetings were held to discuss options for automating a related donor typing process. Ideally, this process would be integrated into the existing NMDP TRAXIS system. The conclusion of these meetings was that an Information Technology Business Analyst must fully scope the project to determine the full impact to all software systems.

Additionally, a work around process to use in the interim was hypothesized. This possible process will be explored in FY10.

II.A. Contingency Preparedness – Hypothesis 3:

NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center.

Aim A.3.1: NMDP Continuity Planning / Disaster Recovery

NMDP Continuity Planning:

The cohesive and efficient operation of the NMDP Network is dependent upon the availability of staff and systems at the Coordinating Center, as well as their resiliency to incidents that negatively impact operations. To help ensure that NMDP operations are able to continue despite operational interrupting events, an Operational Continuity Plan is formally established to mitigate impact from catastrophic incidents by helping to ensure that critical operations continue (or are resumed as quickly as possible) in the event of operational interruptions.

The NMDP's formal Operational Continuity Plan is maintained by the Operational Continuity Planner. The Operational Continuity Planner ensures the proper focus is placed on this important area of operations resiliency and recovery. The Operational Continuity Planner works with each operational unit to determine priorities of work and recovery to accomplish their critical tasks and then works with the Information Technology team to ensure these operational unit needs are incorporated into disaster recovery plans where feasible.

The Operational Continuity Planner provided operational unit representation and operational continuity expertise as a member of the Steering Committee for the two-phase IT Disaster Recovery test conducted in April and May 2009. This allowed IT staff to interface with one person for all operational unit prioritization needs for recovery of software systems and data.

During this period of performance the revamp of the Operational Continuity Plan was finalized and approved by the CEO (plans were initiated to test the plan at the end of this period). Appendices to this plan include the Critical Task List (a prioritized list of essential tasks to continue operations) and the Critical Document Register (a list of essential electronic documents provided by each department and the corresponding location on the network).

To provide essential leadership direction for the prioritization of tasks the Critical Task Review Committee was formed. This committee is scheduled to meet once a year to review updates and additions to the Critical Task List. The committee is chaired by Ray Hornung (Operational Continuity Planner) and consists of Dennis Confer, M.D. (CMO), Mike Boo (COO), Brian Lindberg (VP Legal), Karen Dodson (VP Search), and Cullen Case (Emergency Manager).

Effective communications are essential when responding to any disaster, emergency or operational interruption. The NMDP maintained the Telecommunications Service Priority (TSP) for all telephone circuits from the local vendor servicing the Coordinating Center. TSP ensures NMDP telephone circuits are repaired more quickly than competing commercial facilities

following an outage. The NMDP acquired and distributed through support of the National Communications System 127 Governmental Emergency Telecommunications Service (GETS) cards that allow users to place phone calls during times of significant telephone network congestion. Quarterly user tests were conducted to ensure GETS card accountability and the users' ability to successfully place calls.

Satellite telephones are part of the emergency communications program as a means of last resort to ensure communications during a disaster that impacts landline telecommunications equipment in the United States. Due to ongoing connectivity issues experienced while attempting to use the GlobalStar satellite telephones, the NMDP procured 55 replacement Iridium satellite telephones. Most of these portable telephones were issued to RITN members, and the remaining phones are maintained at the Coordinating Center for use during a disaster. As part of this process all GlobalStar telephones were collected and are stored at the Coordinating Center in the event that GlobalStar is able to fund repairs to its network of satellites. A fixed, "always on" satellite telephone antenna is also installed on the roof of the Coordinating Center to allow incoming and outgoing calls anytime. A similar fixed satellite telephone antenna was also installed at Memorial Sloan-Kettering Cancer Center (a RITN center) because of limited connectivity due to skyscrapers in their vicinity.

To quickly consolidate Network center status reports during a disaster, the WebEOC contract was renewed during this period of performance. WebEOC is a software system which allows all Network centers to provide detailed status information via the Internet. Once submitted, the NMDP will be able to review individual center information or a rollup of the entire Network. This capability will allow NMDP staff to ascertain information such as the number of available BMT beds, available personnel, level of supplies, and other key center operating parameters or issues. During this period of performance the report interface was also updated with assistance from the vendor at no cost to the organization. This new interface was simplified for report submission, consolidation, and review.

NMDP operated donor centers are remote sites that report to the NMDP Coordinating Center. To assist these locations with their resiliency to disasters, small and large, an Operational Continuity Action Guide was created. The guide is a tool to assist managers of these facilities with responding to crisis situations. Sections of the guide include:

- Reporting what and when and to whom
- Local hazards
- How to prepare
- Hurricane
- Flooding
- Earthquake
- Tornado
- Winter storm
- Power outage
- Chemical spills

- Extreme heat
- Important contacts

The Operational Continuity Planner also conducted site visits to multiple NMDP operated donor centers to review the guide with each manager to ensure proper implementation.

Information Technology Infrastructure Disaster Recovery:

NMDP maintains a disaster recovery plan, which is tested annually to verify compliance with operational needs. The results show successful restoration of critical applications and databases during this grant period which has been improved from 96 hours to 48 hours recovery time. The staff assigned to participate in the test and the responsibilities assigned to each staff member during the test were rotated. The plans were refined after each test to aid in subsequent tests or real recoveries. A report summarizing the success and failures of the test was created, including which areas need attention before the next test.

During this grant period, NMDP made several hardware and software purchases to support disaster recovery testing and improve recover times. Additional network segments were also added to support the disaster recovery environment. The following system modifications, upgrades, and tests were performed to help ensure NMDP system recovery:

- To support the growth of the NMDP, the primary data center was moved to a co-location facility at Time Warner Telecom in Minnetonka, MN in FY2008. All of the NMDP's production servers along with the supporting network equipment were moved to the new location. The NMDP still manages all of its network and servers while Time Warner manages the facilities. This move allowed the NMDP to deploy more efficient and effective systems in a stable and controlled environment. The NMDP development environment remains at the Coordinating Center, which now serves as the backup location.

- Purchased, configured and deployed additional network bandwidth. This bandwidth is a prerequisite to remotely operate and manage the site from NMDP's Minneapolis, new data center in a co-location facility at Time Warner Telecom in Minnetonka and New Brighton, MN facilities. This new and consolidated bandwidth also facilitates real time replication of critical data.

- Purchased additional database licenses to allow real-time data replication between the recovery site and the coordinating center.

- NMDP had a regional disaster recovery site, co-located with the Heart of America Donor Center in Leawood, KS. This facility provided a geographically dispersed location for continuity of NMDP information technology operations in the event of a disaster at the Minneapolis, MN Coordinating center. After the primary data center move to Time

Warner Telecom, NMDP closed the Kansas disaster recovery site because of limited capabilities, manageability and capacity issues at that disaster recovery site.

- Equipment still in service in Kansas City was relocated to Minneapolis, MN Coordinating Center to support ongoing disaster recovery activities. In the interim, the NMDP main Coordinating Center currently serves as the primary disaster recovery facility. Completed partial retro fit of coordinating center server room to prepare for disaster recovery test. Replication has been established for critical production components to the backup co-location facility at the Coordinating Center. This replication ensures more rapid recovery times for systems during a disaster. As NMDP operations grow additional systems are continually being added to the primary data center at Time Warner. Any new critical system will also be added to the primary disaster recovery facility.

- Purchased, configured and deployed Storage Area Network (SAN) Disk to centrally manage critical applications and data. One SAN was added to Production data center and the other in Coordinating Center to support ongoing Development and disaster recovery activities. This allows NMDP to move data between sites quickly for recovering critical data and applications.

- Purchased, configured and deployed new hardware to support critical applications for disaster recovery activities. These were significant network and hardware upgrades to maintain and improve NMDP's ability to quickly recover critical data and applications.

- After the Data Center move NMDP conducted periodic disaster recovery tests of its critical systems. Completed the Disaster Recovery Testing for all Tier 1 applications in April 2009. Improved recover time within 48 hour target.

- In addition, the Disaster Recovery Smoke Test for Tier 2 through Tier 4 applications was completed in May 2009 and full Disaster Recovery testing for Tier 2 through 4 applications was successfully completed in June 2009.

II.B. Rapid Identification of Matched Donors – Hypothesis 1:

Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.

Hypothesis 1: Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.

Continued advances in laboratory methods and supporting equipment have positively impacted the level of typing resolution for newly recruited volunteer donors. In 2008, 3 contract laboratories implemented new typing reagents and provided higher than intermediate resolution for HLA-A, B and DRB1. As of December, 2008, 51% of new volunteer donors received higher than intermediate resolution HLA-A, B, and 100% of donors received higher than intermediate resolution DRB1. In October 2008, one laboratory began reporting HLA-C results, in addition to HLA-A, B, and DRB1. As of December 2008, 33% of all newly recruited donors have received HLA-C typing.

Over the past 11 years, the NMDP successfully reduced the cost of HLA typing by over 70% while increasing the resolution and quality (See Table 1 below). The vision and efforts of the Navy to continually press the HLA community in this direction and to lead the advancement and testing of these technologies has been instrumental in achieving these accomplishments.

Table 1. Cost Decreases for HLA-ABDR Typing

Cost Decreases for HLA-ABDR Typing		
Year	**Price (Dollars)**	**Percent Price Decreases**
1997	**$134.75**	**-**
1998	**$73.50**	**45.5%**
2000	**$62.20**	**15.4%**
2002	**$56.02**	**10.0%**
2003	**$53.80**	**4.0%**
2004	**$53.29**	**1.0%**
2006	**$45.78**	**14.1%**
2007	**$45.52**	**0.6%**
2008	**$40.04**	**12.1%**
TOTAL DECREASE	**$94.71**	**70.3%**

If a patient does not find a matched donor and is in urgent need, patient-focused drives can be held and the donor registration process can be expedited, shortening the length of time to listing from 6-8 weeks to 3 weeks. This process includes time to enter demographic data, confirm financial coverage, ship and receive the samples and complete the HLA typing. Demographic data are entered within 72 hours for expedited samples, and they are shipped the next scheduled day, Monday through Thursday. In case of a contingency event, high volumes of samples could be processed and shipped quickly using this established process.

The NMDP's exacting quality control processes have successfully increased the quality of typing received through the contract laboratory network. The method of inserting blind quality control samples into each laboratory's shipment of volunteer donor samples has provided more than 12 years of data tracking the accuracy of high volume typing. Over this time the accuracy rates have continued to improve as documented by decreased monthly error rates and decreased discrepancies as the donors are selected for patients and retyped by other laboratories. The effectiveness of this program and the efforts of a highly qualified high-volume HLA typing laboratory network has resulted in a combined HLA class I and class II QC error rate for this period of 0.09%.

Aim IIB.1.1: Increase Registry Diversity

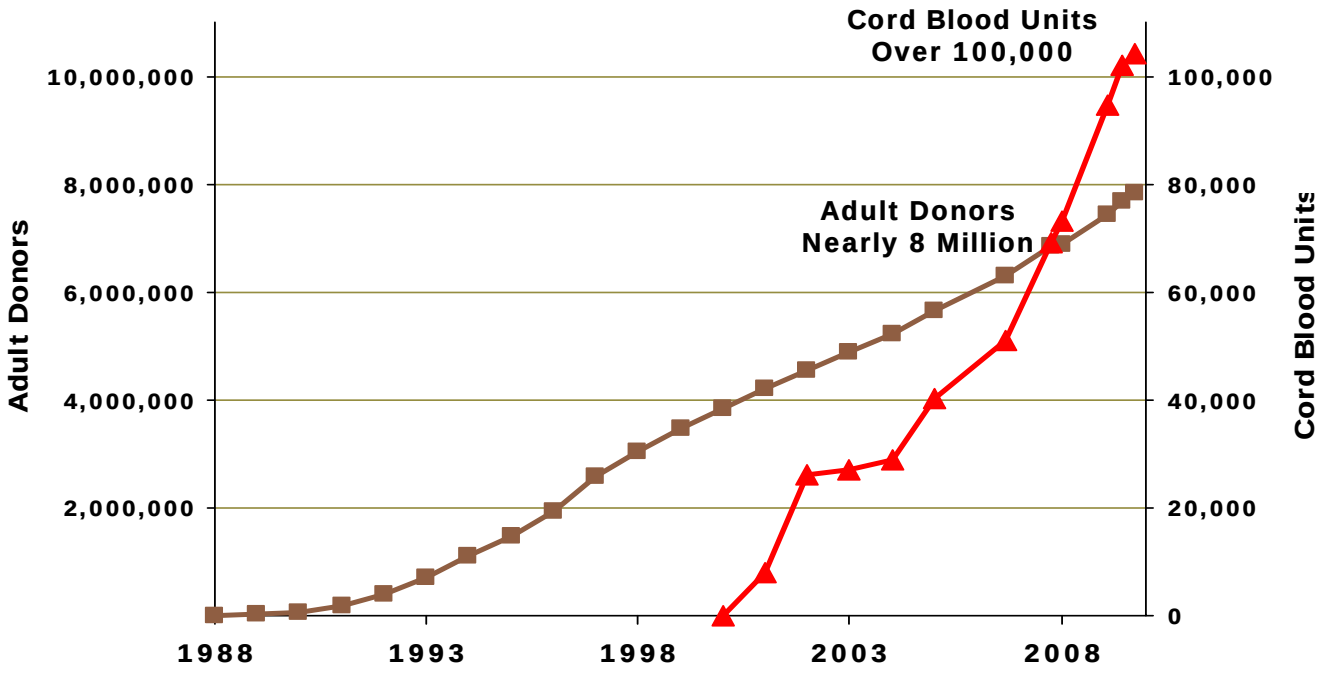
Expand the genetic diversity of the Registry through continued addition of adult donors and cord blood units, utilizing high volume HLA typing methodologies.

During this time period, NMDP donor centers (including DoD) and recruitment groups recruited 374,840 minority race and 407,588 Caucasian donors, which were typed for HLA-A, B and DRB1. Navy funding contributed to the addition of 118,134 of this culturally diverse group of new donors to the Registry.

Advancing technology improved performance
Continued advances in laboratory methods and supporting equipment have positively impacted the level of typing resolution for newly recruited volunteer donors. As of September, 2009

- 84% of new donors received higher than intermediate HLA-A, B typing
- 34% of new donors received intermediate HLA-C typing
- 100% of new donors received higher than intermediate HLA- DRB1 typing

Figure 6. Registry Growth: Adult Donors and Cord Blood Units



HLA Quality Testing

Five HLA typing projects were completed during this contract period. These studies were designed to increase the resolution and quality of HLA typing on the registry to potentially speed donor selection and correctly characterize the match for searching patients, especially from diverse populations. The alleles targeted were ones that repeatedly appeared on the HLA override report as discrepant from previous typing and were described after the initial reporting of typing. Table 2 summarizes the details the typing projects.

Table 2. HLA typing projects summary.

Allele of interest	Previous Type	Broad race	Number of samples	Locus typed
DRB1*1503	DRB1*1501	AFA	249	A, B, DRB1
DRB1*0811	DRB1*0802	NAM	93	A, B, C, DRB1
DRB1*1506	DRB1*1501	API	221	A, B, DRB1
A*3010	A*3002	HIS*	117	A
A*2423	A*2403	NAM	20	A

AFA (Black), NAM (Native American), API (Asian/Pacific Islander), HIS (Hispanic), CAU (White)
* Predominantly HIS, others races were AFA (2), CAU (16), and mixed race (3)

The samples were typed at one lab by DNA methods. The allele of interest was typed by SBT methodologies. In the three DRB1 groups, samples with serologic types at HLA-A and HLA-B

were also retyped by SSOP. The DRB1*0811 group of samples were also typed at HLA-C by SSOP. The updated typing was compared to the initial typing and is summarized in Table 3.

Table 3. Summary of updated typings compared to initial typings.

Allele of interest	% change for allele of interest	% change at A	% change at B
DRB1*1503	79.9	4.9	8.5
DRB1*0811	33.0	3.2	8.6
DRB1*1506	14.0	7.2	11.3
A*3010	87.2	NA	NA
A*2423	70.0	NA	NA

Not all of the samples identified had a stored sample at the repository. Buccal swab kits were sent to adult volunteers identified in the DRB1*1503 group so their typing could be confirmed. In the meantime, to ensure that these samples appear on the appropriate patient searches, the typings identified in the DRB1*1501 and DRB1*0811 groups were re-entered with low resolution typing, DRB1*15XX and DRB1*08XX, respectively, so that Haplogic℠ can accurately calculate the percent likelihood of matching searching patients. The intent is to enter low resolution typing for the A*3010 and A*2423 groups.

Two abstracts detailing results of two of the allele frequency analysis projects were submitted to the American Society for Histocompatibility and Immunogenetics (ASHI) 2009 annual meeting. Both abstracts were accepted for poster presentations.

- African American adult volunteers with DRB1*1501 vs. 1503
- DRB1*0811 in Native American samples typed previously as DRB1*0802 or with codes that include DRB1*0802

Results of these retyping projects improved the HLA typing quality of listed adult volunteers and allows for improved speed of donor selection for patients with these alleles, including non-Caucasian patient searches. These projects highlight the importance of technical oversight of the Registry data and the necessity to upgrade typings routinely in order to provide the most accurate HLA data for searching patients.

STAR II

- The STAR II transaction broker was released in May of 2009. Of note was a change to make the HML processor highly configurable with regard to the database versioning for lab typing kits. This will allow the NMDP to more quickly support new and different typing kits on a lab specific basis, and provides much more flexibility in accepting HLA information from labs for recipients and donors. In addition, this change provides flexibility for management of both operational (patient directed) and research-based lab results.

Adult Donor Registry

- To successfully serve all patients in need of cellular transplantation, the Marketing and Communications Department continued to focus on developing and executing strategies and tactics that help grow the Be The Match Registry℠ by increasing awareness, education, and engagement among target audiences.
- Began developing strategies and tactics for the 2009-2010 Historical Black Colleges and Universities (HBCU) program. The program is an integrated marketing approach designed to build upon earlier work in this college segment to engage HBCU students, faculty, alumni and the broader HBCU community in our mission to save lives, specifically by joining the registry. The program will feature audience-specific awareness and educational tools, including a significant social media component to help ensure outreach to students where they are today.

Developed educational materials

To increase awareness and education about the need for more potential donors to join the registry and the donation process, materials were developed to support registry drive events. These materials are used by our adult donor recruitment teams to engage sponsors in supporting our mission by hosting drive events and to educate drive attendees before, during and after the drive.

- In-language and race/ethnic focused materials were developed in English, Spanish, Portuguese, Chinese, Vietnamese and Korean.
- Primary materials included a Be The Match overview brochure for sponsors, Take the First Step brochure targeting potential registry members, customizable posters and flyers to increase awareness and participation in drive events and a new registry member exit cared which reinforces key messages about the commitment one makes when they join the registry, among many other core materials and tools.

College Channel Programs

- Our recruitment target audience is age 18-44. Colleges and universities provide a large and diverse pool of young and healthy potential donors. Two key marketing programs were developed to target college students: *Get in the Game. Save a Life.* and *Say it Loud. Save Lives and Be Proud.*
- Get in the Game. Save a Life was designed to educate college football athletes at targeted colleges and universities and encourage them and their community to join the registry. Over 8,000 new members were added to the registry during spring camp recruitment events at 29 institutions across the country.
- Say it Loud. Save Lives and Be Proud was designed to target students at Historically Black Colleges and Universities (HBCUs). Audience-specific materials were developed to educate and engage the students on campus and the faculty, alumni and broader HBCU community. A key component of the program was the launch of a Be The Match Web site on the premiere online medium for HBCU students --- hbcu.bethematch.org. The

program was launched in November 2009 and about 2,000 new members have been added to the registry thus far.

Aim B.1.2: Evaluate HLA-DRB1 High Res Typing

No funding was requested under this Aim for the 0058 budget cycle.

Beginning in August 2008, the donor recruitment typing laboratories began submitting high resolution HLA-DRB1 results using high definition One Lambda sequencing kits. As a result, DRB1-locus specific customized typing requests from June-December have decreased by 20%.

Aim B.1.3: Evaluate HLA-C Typing of Donors

No funding was requested under this Aim for the 0058 budget cycle.

To further understand the impact of providing HLA-C typing in addition to HLA-A, -B, and –DRB1 at the time of recruitment, patient-directed requests made to 5,398 newly recruited male volunteer donors between the ages of 18-30 years were evaluated. HLA-C was randomly added to 3,291 of the donors (61%). Class I HLA-A, -B and -C typing results were 75-80% allele level and class II DRB1 typing results were 97% allele level. The donors with and without HLA-C were evaluated two years after joining the Be The Match Registry. Donors with HLA-C typing were selected 1.9 (n=147), 1.6 (n=21), and 1.9 (n=23) times more often for Confirmatory Testing (CT), HR, and WU, respectively, than donors without HLA-C typing. Although P values for Pearson's Chi square tests at 95% confidence were not statistically significant, an increase in patient-directed activity has trended toward significance as time has passed, for the cohort with C typing. Adding HLA-C typing to male donors between the ages of 18-30 years at the time of recruitment increases the likelihood of the donor being selected by a searching patient and donating adult stem cells.

This study was presented for poster presentation at the 2009 annual meeting of the American Society for Histocompatibility and Immunogenetics (ASHI): "Impact of Adding HLA-C at the Time of Donor Recruitment on Future Patient-Directed Requests."[4]

Aim B.1.4: Evaluate the suitability of buccal swabs as a method to collect DNA samples to HLA type casualties and potential related donors in contingency situations, and to obtain research samples.

The initial phase of the Sample Storage Research Study was executed in September 2007. Blood and buccal swabs were collected from 30 current and fully HLA characterized volunteer quality control donors. Study samples required for the 5-year study were prepared and stored at the NMDP Repository. Fresh blood, blood spotted onto Whatman® 903 filter paper and buccal swabs for each donor were sent to two laboratories to initiate the study (Time Point Zero) in September

2007. One laboratory was contracted to perform high resolution typing for HLA-A, B, C, DRB1, and DQB1 loci. The second laboratory was contracted to perform intermediate resolution typing for HLA-A, B, C, and DRB1 loci. The second laboratory was also contracted to evaluate the quantity and quality of DNA within each sample type. Complete results were received from each of the two laboratories. All typing results were 100% accurate, and the evaluation of the DNA was complete and thorough. The results from Time Point Zero are the basis for determining the stability and usefulness of the DNA stored in each sample type for the next 5 years. Results from this study will provide key quality parameters for NMDP operational decisions concerning sample storage and may also contribute sample storage guidelines for other registries.

Stored donor samples were sent to the laboratories at Time Point 1 Year in September 2008, and for Time Point 2 years in September 2009. All HLA results were 100% accurate for each time point. One measure of the quality of the stored samples is the frequency of repeated HLA testing.

- The laboratory performing intermediate resolution HLA-A, B, C and DRB1 reported zero repeats.
- The laboratory performing high resolution HLA-A, B, C, DRB1, DQB1 reported the following repeats:

Table 4. Summary of repeat testing required by sample type.

Sample Type	Time Point		
	Zero	**1 Year**	**2 Year**
Blood	3	0	2
Blood Spotted onto Filter Paper	2	0	1
Swabs	2	0	4
% of Total loci tested	4.6%	0.0%	4.0%

The 6 laboratories currently performing HLA typing on new donor recruitment samples report a donor sample repeat rate between 3-5 % of loci tested for buccal swab samples received each week.

Aim B.1.5: Evaluate the factors of donor utilization and speed of search process after strategic upgrading of selected adult volunteer donors.

Prospective HLA Typing of HLA-A, B-Only Typed Donors-Formal Searches
In this study, HLA-A, B only typed donors were identified for prospective HLA typing upgrade for current patient searches for which there were relatively few HLA-A, B, DRB1 matched

donors. 691 donors were selected and HLA typing upgraded to intermediate resolution HLA-A, B, C, and DRB1. Donors were monitored for future patient-directed activation events. Current follow-up of these donors revealed the activation of 9 donors for CT requests, followed by 2 workup requests and subsequent stem cell donations. This systematic strategy of identifying donors likely to match searching patients appears promising. Continued application and extension of this strategy in the context of preliminary searches may allow optimization of these efforts to benefit many future patients.

P**reliminary Search / Donor Contact project (minority donor sub-group):** The NMDP Call-Back Unit piloted an effort to contact domestic donors appearing on preliminary searches, to assess availability. From a list of 3000 confirmed available donors, the Scientific Services Search Strategy team selected a group of 422 minority donors whose HLA typings would benefit by selective locus-specific HLA typing upgrades. The prospective typing of these minority donors was completed in late October 2008. Current follow-up of these donors for patient-directed activation events revealed the activation of 3 donors for CT requests.

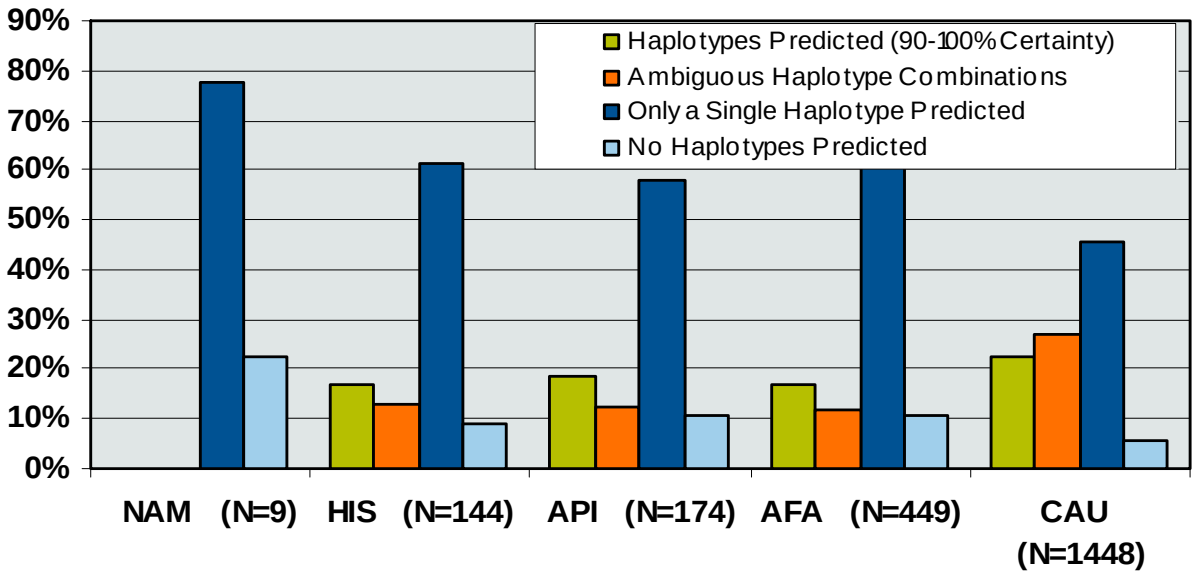
Based upon the current results, it was determined that moving forward with such a strategy would be of only minimal benefit to future patients, and will not be pursued further.

Further Analysis of Patient Phenotype Categories with No Potential Donor Options
The systematic evaluation of potential donor options for 118,673 patient HLA phenotypes evaluated in the Optimal Donor study revealed 2,191 unique patient phenotype categories (2,225 patients) that did not have a potential broad serologic-level match within the HLA-A, B, DRB1 typed donor pool. The HLA-A, B-only typed donors in the Registry were evaluated to assess potential donor options for this patient pool.

The NMDP Registry contains approximately 743,000 HLA-A, B only typed donors. Less than 0.4% of these donors (N=2972) are activated by transplant centers each year and less than 0.1% (N=2) of this activated donor subset moves forward to donate a stem cell product. In an effort to improve the utility of HLA-A, B only typed donors, a strategy was evaluated to identify donors who may potentially match future patients with uncommon phenotypes and upgrade their HLA typing on the Registry.

An analysis of patient haplotype predictions provided a collective picture of various factors resulting in unavailability of potentially matching unrelated donors in the Registry (Figure 7).

Figure 7. Patient Haplotype Predictions by Race



Patient HLA-A, B phenotypes were used to search for potential HLA-A, B matches from a subset of 30,924 donors carrying less common HLA-A, B phenotypes.

- 4,914 donors with unique HLA-A, B only phenotypes that were not represented in the HLA-A, B, DRB1 typed donor population (singletons).
- 26,010 donors found in distinct HLA-A, B only phenotype categories that were found to contain 2-10 donors each

Intermediate-high resolution HLA-A, B, C, DRB1, and DQB1 typing was performed on selected donors. Prospectively-typed donors were monitored for patient-directed activity.

A comparison of patient and donor typings resulted in the identification of 805 donors from the singleton category and 4,126 donors from the 2-10 copy category that shared HLA-A, B phenotypes with patients in the study group. 1,359 donors with available repository samples were selected for prospective HLA typing (Table 5).

Table 5. Summary of HLA-A, B only typed donors matching searching patients with no available HLA-A, B, DRB1 matches on the registry.

HLA-A, B Only Donors	Unique Split-Serologic Phenotype Categories - Copy Number	
	1	2-10
Total	4,914	26,010
Potentially Matched	805	4,126
Prospectively HLA Typed	205	1154

Current follow-up of prospectively typed donors for patient-directed activation events revealed the selection of **12 donors for CT requests** on behalf of 11 different patients (Table 6).

Table 6. CT requests by HLA-A, B only donor phenotype category.

AB Only Donor Phenotype Category	Singleton	2-10 (2)	2-10 (3)	2-10 (4)	2-10 (7)	2-10 (8)	2-10 (10)
Activated Donor Count	1	1	1	2	2	2	3

- The activated donors had been on the registry from 8-14.9 years prior to selection for HLA typing through the project
- Donors were activated for new patients within an average of 295 days from the date upgraded HLA typing results were available to searching patients
- Approximately **0.88%** of the HLA-A, B only typed donors identified by the project were activated by searching patients, an increase of about 2-fold compared to Registry norms. This is a stimulating finding in context of a typing strategy using both patients and donors with less-common HLA phenotypes.
- One donor went on to donate a stem cell product for an African American patient who had an active donor search for almost two years. The African American donor was a 9/10 allele match with the patient.

This systematic strategy of identifying donors likely to match searching patients appears promising. Continued application and extension of this strategy may allow optimization of efforts to benefit many more patients.

The results of the analysis were presented as a poster presentation at the 2009 ASHI annual meeting.[5]

Aim B.1.6: Maintain a comprehensive quality control program

The NMDP's comprehensive quality control program has supported the successful increase in the quality of HLA typing received through the contract laboratory network. Blind Quality Control (QC) samples are added to each weekly shipment of new donor recruitment samples. These QC samples comprise 2.5% of each shipment, and must be indistinguishable from the donor samples. Immortalized B-Lymphocytic cell line (B-LCL) cells are applied to cotton-tipped swabs and included as QC in shipments of buccal swab donor samples. The Research Sample Repository contains frozen cells from thousands of fully HLA-characterized donors and recipients. QC swabs are created by the Repository staff from expanded B-LCL vials chosen from this resource.

To evaluate the storage stability of the B-LCL swabs, a QC component was included in the Sample Storage Research Study described above. B-LCL swabs from 10 fully HLA-characterized unique cell lines were created and stored as described for the donor samples. Sufficient QC samples were created to support an 18 month study. HLA typing and DNA evaluation was performed the same as described above for the donor samples. B-LCL swabs were sent to the HLA testing laboratories for: Time Point Zero in December 2007, Time point 6 Months in June 2008, Time Point 1 Year in December 2008, and Time Point 18 Months in June 2009. HLA results from each time point were 100% accurate for intermediate and high resolution typing. The DNA quality was excellent and the quantity sufficient for HLA testing from all 10 samples. One sample from the Time Point 18 Months needed repeating for HLA-DQB1. The QC portion of the Sample Storage Research Study is complete.

New QC master HLA types were added to the inventory of QC samples available for inclusion in recruitment and customized typing shipments.

- 66 new volunteer donors were recruited to add HLA diversity to the QC program. A portion of the collected blood samples were spotted onto filter paper and the remainder aliquoted and frozen for future use. High resolution HLA-A, B, C, DRB1, DQB1, and DPB1 typing was performed on a sample from each volunteer. For volunteers that are also on the registry, these results were used to update their registry typings.
- 180 new and unique B-LCL samples were expanded to provide cells for the creation of B-LCL QC swabs.

II.B. Rapid Identification of Matched Donors – Hypothesis 2:

Primary DNA typing data can be used within the registry to improve the quality and resolution of volunteer donor HLA assignments.

Aim B.2.1: Collection of Primary Data

In this grant period a new SBT reporting format that includes gSSP results (ambiguity resolution using SBT) was proposed. (Interpretation of SBT is implemented as an up-front technique.) A series of conference calls were held to discuss the SBT reporting format and provisions for using SBT for ambiguity resolution. By the end of the year, one laboratory was sending test messages in the new format.

Development of new reporting formats that meet the needs of the HIEDFS (HLA Information Exchange Data Format Standards) consortium continued through the year with an in-person meeting at the EFI conference to review the draft standard and make enhancements

Aim B.2.2: Validation of Logic of Primary Data

No funding was requested under this Aim for the 0058 budget cycle.

Aim B.2.3: Reinterpretation of Primary Data

Reinterpretation of primary data to improve the level of resolution of previously reported donor typings.

No funding was requested under this Aim for the 0058 budget cycle.

Aim B.2.4: Genotype Lists & Matching Algorithm

No funding was requested under this Aim for the 0058 budget cycle.

The theory underlying this Aim was that the interpretation of the primary data into genotype lists and the utilization of these instead of search determinants could provide a more rapid and more specific matching logic. The genotype list database developed as a result of this Aim has been used as the foundation for a new matching algorithm HapLogic that directly applies DNA typings of any complexity into the up-front search.

II.B. Rapid Identification of Matched Donors – Hypothesis 3:

Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor.

Aim B.3.1: Phase I of EM Haplotype Logic

No funding was requested under this Aim for the 0058 budget cycle.

HapLogic Algorithm
Based on the design, validation, and testing of the HapLogic II algorithm, it was decided that HapLogic II would not be able to implement 8/8 and 10/10 predictions or a new sort based on those calculations. These elements are planned for the HapLogic III phase. Without a change to the sort order, comparing HapLogic I vs HapLogic II was not possible and again will be considered after HapLogic III changes, as well as a repeat TC satisfaction survey.

Aim B.3.2: Enhancement of EM Algorithm

During this grant period, the EM Algorithm was enhanced and used in order to prepare a manuscript entitled "Re-creation of the Genetic Composition of a Founder Population," which was submitted and accepted by Human Genetics.[6] Three abstracts were submitted to ASHI (2 accepted for poster, 1 for oral presentation) on haplotype analysis of the NMDP registry.[7,8] Three abstracts were submitted and presented at the 15th IHIWS conference ("High resolution reconstruction of HLA haplotypes in Native Americans," "HLA haplotype diversity in Brazil" and "Anthropological Insights from a Novel Visualization and Clustering Tool for HLA Haplotypes and Populations."

Much of this work is foundational to future development of high-resolution haplotype estimation from the entire registry which is critical for moving HapLogic forward in terms of being able to present donors sorted according to overall likelihood of 8/8 and 10/10 allele match which is now the clinical standard.

Aim B.3.3: Optimal Registry Size Analysis

During this year, study design work was done on the clinical validation of 8/8 matching rate predictions. The study will select a random set of 250 Caucasian donors, to be used as pseudo-patients, for donor selection and typing to determine the likelihood of finding an 8/8 HLA match for each pseudo-patient on the registry. The study design work also led to statistical power

computations to identify the confidence intervals around the point-estimates of match rates for different numbers of patients. The NMDP secured study participation commitments from the DKMS and DoD ensuring access to the vast majority of donors on these searches.

Aim B.3.4: Target Under-represented Phenotypes

The objective of this project was to link donor zip code information with HLA variables including haplotype assignments, and integrates them into standard Geographic Information Systems (GIS) software for visualization.

The progress made this year included selection of GIS software (ESRI) for use in generating true geographical encoding of donors under this aim. In order to move forward with this aim:

- Staff were sent to the annual GIS software (ESRI) user-group meeting
- GIS software was purchased and installed along with census resource databases
- A prototype kernel density (heat) map was produced to show the geographical distribution of the most common African American broad HLA phenotype.
- A full ZIP code update was performed on the geocoding database for use in ongoing ad-hoc analyses

Additionally, a model of genetic diversity (based on census population within recruitment regions) was proposed and accepted as part of the 5 year recruitment plan for measuring diversity goals

Aim B.3.5: Bioinformatics Web Site

No funding was requested under this Aim for the 0058 budget cycle.

Aim B.3.6: Maximize software using consultant data

The expert HLA advisors were an integral part of the continued validation of HapLogic in the Traxis application and have contributed ideas for the future design planning additional enhancements to the HapLogic algorithm.

Search Strategy Advice (SSA) program
The SSA program offers HLA search strategy recommendations for any TC that requests the free service. The program uses external and internal HLA experts to write reports summarizing a search strategy for each patient to help the TC identify the best stem cell source for their patient.

Search strategy skills were developed by internal staff with HLA expertise and CHTC certification. Both internal and external experts participate in a rigorous QC program.

The SSA program completed 1593 search strategy advice reports for 114 transplant centers in this period, which included 742 (47%) reviews by internal advisors and 851 (53%) by external advisors. The required turnaround time was 5 business days for the program, the actual was 3.9.

SSA Principal Investigator Meeting

A principal investigators' meeting was held in which all external advisors and internal advisors participated. Best practices were discussed along with future changes including: HapLogic III, HLA nomenclature, future cord blood registry data integrations, and discussed HLA research topics and data.

II.B. Rapid Identification of Matched Donors – Hypothesis 4:

Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.

Aim B.4.1: Expand Network Communications

During the grant period, the IT department focused on support of the processes and tools utilized by the Search and Transplant department at NMDP. This was accomplished by developing efficient modifications to systems, processes, and reporting capabilities, as well as ongoing enhancements of the applications. These applications and enhancements allow for increased speed and accuracy in the exchange of data transactions in the processes of identifying the best potentially matched donor or CBU. In addition, the collection of research data was essential for research studies to improve the clinical outcome for the patients.

Traxis
Traxis was upgraded to address defects related to patient look ups and email notifications (sending them to NMDP Search Coordinators when a search request was processed).

- The TRANS Link® application was retired on May 31, 2008. Future reporting will only be under the Traxis application.
- Traxis™ application was released in production March 17th, 2008. Traxis is the NMDP's fully-integrated search management interface. This web-based application is used by transplant centers to manage and track the entire search process, to access unrelated adult donors and cord blood units worldwide, from initial search to transplantation. Traxis combines multiple functions, allowing users to perform searches, request HLA typing, manage their workflow, request work-ups, and perform multi-cord searches. Traxis incorporates a host of time-saving features designed to improve accuracy and simplify the search management process. It offers the electronic workup or cord order request feature and a better user interface. This application replaced the current TRANS Link application.
- 137 centers, both domestic (123) and international (14), comprising 325 users have switched from the old TRANS Link application to the new Traxis application.
- Traxis was upgraded on June 14th, 2008 to fix defect and performance issues identified during the first two months of use.

SEARCH Link
To aid the Search and Transplant Department in maintaining patient safety, the following were accomplished:

- A preview button was added to provide the search coordinator easier access for validating electronic workup requests submitted by the transplant center prior to activation. Donor workup and cord order requests are now highlighted in pink for easier identification. New reports improving operational efficiencies for the search coordinators have been added;
    - Working TC Cord Request Report contains updated delivery instructions and/or contact names for the transplant center's cord shipment request;
    - Working TC Donor Request Report contains updated data for Marrow Collection, PBSC Collection, Pre-Collection Samples, Day of Collection Samples, Product Tag Information, and/or Comments for the transplant center's workup request.
- The ability to activate Electronic Workup requests initiated from the NMDP Traxis™ application was implemented. Process improvements were incorporated by allowing search coordinators the ability to change the product selection after the transplant centers' initial request.
- To help transplant centers and the Search and Transplant Services department facilitate the search and determine the best match for patients, the Workflow Management Reports were updated with HLA-C and -DQB1 probability calculations.
- Actions Codes were implemented for Cooperative Registry Donors and CBUs to improve operational efficiencies. These codes will function like the domestic donors and CBUs. Some Action Codes were retired.
- The Working TC Request tab no longer displays on the Request Detail screen for Rejected Electronic Workup requests.
- The Request Detail date fields for rejected requests are grayed out and made not editable to eliminate accidental changes.
- Requests for the same source in the search detail screen will continue to sort by date, with the most recent date displaying first. If there are multiple requests for the same source on the same day, the requests will sort in the following status order: 1.) Pending requests 2.) Open requests 3.) Resolved requests 4.) Closed requests 5.) Rejected requests.
- Functionality was restored to display a pop-up window indicating active sources exist on a search if a user attempts to cancel the search for a source type. The search will not be cancelled.
- Donor Information Infectious Disease Markers (IDMs) screen and Donor Information Report.
- Added additional tests: Chagas (screening) and Chagas (confirmatory), along with their results and test dates performed.
- Revisions to the Form 24 v12.0 and Form 50 v13.0 resulted in:
    - Text change for CMV Total to Anti-CMV Total
    - Results changed for Anti-CMV Total from Not Performed, Positive, Negative, and Prev. Positive to Not Performed, Reactive, Non-reactive, and Prev. Reactive
    - Interpretation of IDM test results was changed from "Interpretation information for infectious disease marker (IDM) testing is available on the NMDP Network Website" to "Interpretation information for infectious disease marker (IDM) test results is available on the NMDP Network Web site."

  - Cord Information Maternal Infectious Disease Marker screen and Cord Information (Detailed and Summary) and Cord Lab Summary Reports
  - The Chagas EIA test text was changed to Chagas (screening)
  - The RIPA (confirmatory) test was changed to Chagas (confirmatory)

- Restored the display of Release Codes for released donors on the Potential Donor List and 110A reports
- Electronic Workup
  - Validation rules for the Day of Collection Samples section was added as follows:
    - If marrow and/or PBSC is requested or patient is on PBSC vs. Marrow randomized trial, the tubes of peripheral blood listed under Day 1(marrow and PBSC) must total at least 7 ml when added together.
    - If PBSC is requested or patient is on PBSC vs. Marrow randomized trial, the tubes of peripheral blood listed under Day 2(PBSC only) must total at least 7 ml when added together.
  - A pop-up warning was added to display when the selected source could be one and the same as the patient based on birth date, sex, and match grades

- To improve operational efficiencies for the Search and Transplant Department:
  - Find feature was implemented to easily filter patients with Coop action items.
  - The Email field was implemented as required in the User Maintenance screen when adding a new user or making edits to an existing user.

To facilitate best donor/CBU matches for transplant centers and for the Search and Transplant Services department:

- Functionality was restored to display match grades for manually entered Cooperative Registry Donors and CBUs.
- Functionality was restored to set the status of Cooperative Registry Cords released as infused to NA.
- Functionality was restored to display Cooperative Registry Cord and Donor IDs, along with the Action Code descriptions, if applicable, in the confirm multiple selection pop-up when multiple sources are released.
- Functionality was restored to prohibit an international transplant center to request a CBU from an international cord blood bank. Cord Blood Bank 191, StemCyte Taiwan National Cord Blood Center, is an exception to this rule.
- Two-day PBSC collections are shown as one donation on the Donor Info screen under Prev. Donations to lessen confusion.

STAR II

To increase operational efficiencies for the Search and Transplant Department:
Action codes that are no longer active/utilized were retired

To increase the reliability and timeliness of notifying network members of search activity,

improvements were made in the functionality to send data to member centers. These improvements will increase the system capacity for handling large transaction volumes and detect data integrity issues (like incoming & outgoing duplicate transactions, gaps in sequence numbers).

- To aid the Search and Transplant Department in maintaining patient safety, functionality to improve reliability of persisting typings for new donors was deployed.
- To increase the reliability and timeliness of notifying members of search activity, functionality to improve reliability in sending data to member centers. This was done by improving error handling of transaction delivery client was deployed.
- Efforts were focused on the analysis and realization of request/fulfillment messaging and storage. This foundation (data model & integration) is a prerequisite for implementing improved electronic communication and parallel search stages.
- Analysis and vetting of request/fulfillment messaging structure through peer-to-peer (P2P) message realization.
- Analysis and vetting of request/fulfillment storage model.

Do It Yourself (DIY) and STAR Link Web Donor Recruitment enhancements:
Do It Yourself (DIY) application project work efforts delivered the following functionality to allow Donor Centers and Recruitment Groups to use DIY as a recruitment tool:

- Automation of Drive request by DC/RG's – formerly, recruiters filled out a drive request in SLW, and then faxed in the request. Staff would manually approve these drives.
- Ability to create single use promotional codes and create estimates for a drive.
- Ability to set up multiple funding sources in a single drive. Example: CMF donor paid in which donor pays $25.00, or CMF sponsor paid, in which a sponsor is billed and the donor responsibility is $0.
- Prioritization and automation of funding sources which allows recruiters to choose which funding type should be charged first.
- Added functionality including Stage Drive, Cancel Drive, Estimate Status and Date, and View of actual against estimates via the Drive Estimates Grid.
- Setting Drive types: This allowed for automation of "Live" drives as well.
- Drive estimates automatically updating in FDR.
- Automated status of donors including staged, newly entered, or duplicate.
- Create unique "single use codes" - ability to have SLW automatically generate X number of unique codes for a single drive, with the added functionality to export these promotional codes to a spreadsheet for mail merge.
- Drive max for Caucasian and overall drive totals.
- Automatic invoicing of newly entered donors.
- Automation of emails for kit returned, no kit received, and pending deletion due to incomplete registration in 45 and 60 days.
- User Interface (UI) changes for Pending Donor and Pending Drive including new functionality of screens for additional edits.
- Automation of triggers to send emails to donor, email sent after 5, 10, and 15 days.

- Interface changes such as "Verisign" logo.
  Reports that will allow tracking of donor recruitment and the supporting activities:
  - Drive Activity Reports
  - CSS Activity Reports
  - Drive Detail Report

FDR

- FDR will get new pushes of data from STAR Link via transactions. This new interaction will eliminate the need to send a Drive Detail report via email to the FDR user and will replace the "keying" of drive estimates.
- Changing the invoicing frequency due to length of drive. Drives longer than 12 days will invoice only monthly compared to the standard weekly.

Statistic: DIY Online Donor Registration through www.marrow.org resulted in a **total of 75,077** between 1/1/08 – 9/30/09.

Aim IIB.4.2: Central Contingency Management

Custom Search Support (CSS) uses trained NMDP coordinating center staff to provide comprehensive donor/cord selection recommendations and patient search monitoring on behalf of the TC staff. Network member centers have the option to use this service, where as it is required for low volume centers and non-network centers. Navy funds supported the expansion of the CSS service as it increased NMDP's capabilities to provide centralized rapid turnaround search support in the event of a contingency event.

Efforts to educate and expand the service to additional TCs included:

2009 Tandem (ASBMT/CIBMTR) meeting: a physician education session was held for the CSS program. TC medical directors were contacted to arrange meetings with CSS staff. The targeted centers were TC's that had:

- expressed interest in the program,
- staff turnover,
- increased transplant activity, or
- TC coordinators who were struggling with work volume

Five scheduled physician information meetings were held to assess interest. Four of these requested follow-up activity. The NMDP booth promoted the service by offering CSS educational materials and CSS staff was available to discuss the service.

Four network transplant centers began using the service during this period. NMDP staff continued to provide CSS information to TCs that had made inquiries about the program.

Developed and Disseminated Clinical Guidelines for Evidence-Based Decision-Making

To improve appropriate application of transplantation in the treatment continuum and to support efficient and proactive post-transplant care, a tool kit "*Quick-Reference Guidelines for Transplant Consultation and Post-Transplant*" was created and disseminated in print and online at: http://www.marrow.org/md-guidelines. By combining "*Recommended Timing for Transplant Consultation*" and "*Long-Term Care Guidelines*" (which includes GVHD screening and photo atlas) into one tool kit, clinicians have a resource available to quickly access to support their decision-making.

Two efforts to disseminate the guidelines were implemented:

- The first was a direct mail and e-mail notification. Response was modest (11% of NMDP Network transplant centers ordered), but the guidelines continued to gain wider use over time.
- A second mailing was undertaken following a re-design that provided a copy of the tool kit to each physician at NMDP Network Transplant Centers. Clinician feedback had indicated a preference for receiving a physical copy before ordering a larger quantity (vs. a descriptive mailer). Response to this second effort was higher, with more than 30% of centers responding (program is still underway).

Developed and Disseminated Educational Resources on Advances in Transplantation

To continually increase awareness and application of transplantation research, educational resources for physicians who refer for transplantation were developed.

- *Advances in Transplantation* Special Print Edition newsletter, which highlighted key research presented at major conferences, was disseminated to more than 10,000 U.S. clinicians. The newsletter is also available online and via e-mail, to subscribers of the bi-monthly e-news version at: http://www.marrow.org/md-news.
- A fact sheet on *Outcomes in Unrelated Hematopoietic Cell Transplantation* summarizes key trends in transplantation in order to provide referring and transplant physicians with the most critical factors affecting improved survival in transplantation. The fact sheet will be disseminated to more than 10,000 U.S. clinicians and can be found online at: http://www.marrow.org/md-clinicalfacts.

Assessed Need and Developed Plan for Dedicated Transplant Center Web Resource Center

To increase current and effective communications between NMDP and Network Transplant centers, an assessment of needs for online communication was conducted with NMDP staff and with transplant center personnel. Based on the assessment, an initial project definition has been developed. A review of the proposed plan is underway and recommendations will be made for implementation.

Aim B.4.3 Conduct a transplant center benchmarking analysis to identify center-specific factors (e.g., quality management techniques and processes) that contribute meaningfully to superior survival outcomes. Share processes that contribute to superior outcomes with the entire TC network as best practices.

After submission of the statement of work, this project was deemed as lower priority and no funding was assigned. This aim will be re-evaluated in future proposals.

Aim B.4.4 Identify plans to expand capabilities of collection center and apheresis center network to meet increasing number of donor product requests on both a short-term and long-term basis.

In 2008, NMDP contracted with American Healthcare Solutions (AHS) to assess ways in which the NMDP could increase availability and accessibility of product collection centers (Apheresis Centers and Marrow Collection Centers) in order to meet current situational needs and to prepare for future growth objectives. AHS subcontracted with Life Science Strategy Group (LSSG) for completion of the majority of the tactical planning and subsequent deliverables. On June 6, 2009, a Phase III Final Report was provided to the NMDP AC/CC Expansion team charged with examining possible strategies to increase collection capacity. The Final Report provided recommendations for successful implementation of the original strategy for recognition of the apheresis and collection centers.

To summarize, the original initiatives discussed between LSSG and the NMDP AC/CC Expansion Team included:

- Web-based Scheduling for product collections
- DC/AC/CC Tiers
- AC/CC Recognition and Incentive Program
- Payment for AC/CC Collection Coordination
- Standardization of DC/AC/CC Procedures of Interaction
- Review NMDP Product Cryopreservation Policy.

Update on the original initiatives:

Web-based Scheduling for product collections has become an exploratory project for one of the NMDP-Operated Donor centers, and will be analyzed in a pilot project launched by that team during late summer/early fall 2010.

Physician staff at NMDP determined that no changes should be made to the current Product Cryopreservation Policy at NMDP in the absence of a clinical study group convening to determine patient and product safety issues as well as transplant center customer issues.

The remaining four initiatives left for the AC/CC Expansion Team were altered slightly to better provide a solution to the issue for which they were developed. These included:

- AC/CC Regionalization project
- AC/CC Recognition
- Visibility in reimbursement with potential for coordinated payment for cancellations / postponements
- Standardization of Procedures of Interaction

The LSSG Final Report focused on establishing a program to recognize the contributions of the AC and CC groups working with the NMDP. Members of the NMDP AC/CC Expansion team developed a robust and comprehensive plan for center recognition based on the recommendations from LSSG. Implementation options, including budget considerations, are being considered.

Additionally, the AC/CC Expansion team has developed a proposal for regionalization of current collection sites; however the plan is pending based on a need for implementation. To date, the majority of growth in collections has occurred organically without significant NMDP intervention. If it becomes necessary to implement a regionalized model, the plan is available.

Finance documents that describe fees and reimbursement for product collection have been updated and are now more comprehensive and descriptive so as to make clearer what is reimbursable and at what rate. The NMDP Membership group will continue working with NMDP finance staff to identify new opportunities for adjusting fees and defining services so reimbursement is as transparent as possible for the ACs and CCs that collect product for the NMDP.

Finally, the Universal Procedures of Interaction (U-POI) have been developed and were implemented in March of 2010. To date, U-POI have been developed for nearly every DC to AC and DC to CC relationship in the NMDP Network, with the expectation one will be in place prior to any product collection collaboration between a DC and corresponding AC or CC.

II.C. Immunogenetic Studies – Hypothesis 1:

HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations it will not be possible to delay transplant until a perfectly matched donor can be found.

Aim C.1.1: Donor Recipient Pair Project

A retrospective Donor/Recipient (D/R) Pair HLA typing project to perform high resolution class I (HLA-A, B, and C) and class II (HLA-DRB and DQB1) typing of paired samples from NMDP's Repository, was initiated in 1994. The primary objectives of the Donor/Recipient Pair Project are to:

- Determine the impact of DNA-based HLA matching on unrelated donor transplant outcome
- Develop strategies for optimal HLA matching
- Evaluate the impact of matching at alternative HLA loci on transplant outcome
- Promote the development of DNA-based high resolution HLA typing methodologies

Transplant pairs were chosen from stored samples at the NMDP Research Sample Repository and distributed to participating laboratories for high resolution HLA typing. All paired samples are selected in collaboration with the Center for International Blood and Marrow Transplant Research (CIBMTR) Statistical Center to ensure the additional cases would benefit ongoing and future analyses. The cohorts tested during the project period consisted mainly of transplants that utilized peripheral blood stem cells as the cell source, reduced intensity or non-myeloablative preparative regimens, rare diseases and older patients reflecting the expanding indications for unrelated donor HSCT. In addition, the project has added cord blood transplant pair samples to facilitate studies of HLA matching in this high growth field.

Testing was completed on an additional 1,047 donor/recipient and 126 cord/recipient pairs during the project period, bringing the total enrolled to over 14,000. Typing results were reported electronically to the NMDP and compared with previous transplant center results as a measure of quality control. At the initiation of the project period five laboratories participated in the project. Following a competitive bid processes the laboratory network was reduced from five to four laboratories, due to decreased typing volumes and to achieve volume-based price breaks. Typing at the DQA1 locus was halted due to the greater than 98% linkage seen with DQB1. The subsequent cost reduction permitted the addition of presence/absence KIR genotyping on 2DL1-5, 2DS1-5, 3DL1-3 and 3DS1 with no incremental costs to the budget on all 1173 paired samples.

In order to continuously upgrade the Donor/Recipient Pairs Project, an evaluation of typing issues on all inactive pairs was performed. A group of samples were compiled, all with outstanding typing issues ranging from dead locks between the typing lab and either the quality control lab or the transplant center; suspicious DQA1 and DQB1 based linkages, and audited typings that did not match updated typings by the transplant centers. These samples were distributed to a tie-breaker laboratory for final resolution. All results were reported and resolution of over 250 pairs was achieved.

Current HLA matching guidelines for unrelated HCT recommend avoidance of mismatches only within the antigen recognition site, i.e. exons 2 and 3 for HLA class I and exon 2 for HLA class II. This recommendation is based on the hypothesis that amino acid differences outside the antigen recognition site are not immunogenic. There is little functional data available to prove this hypothesis and clinical analysis would require an unattainable data set to reach significance as previously reported.[9] In brief, an investigation of DRB1*140101 and *1454 mismatches was performed. From a pool of 4222 8/8 matched European American donor/recipient transplant pairs in the NMDP database, only 102 pairs were identified that carried the unresolved DRB1*1401/DRB1*1454 with matching at class I loci. The DRB3 linkage was used to identify 12 pairs likely to be mismatched for DRB1*140101/DRB1*1454, but was determined an insufficient sample size to assess the impact of the mismatch on transplant outcome.

The Antigen Recognition Site Allo-reactivity Assessment Project will give insight into the allowable tolerance of matching needed outside of this binding region. Specific queries of the Be The Match Registry allowed for selection of ninety-nine potential donors from 4 of the 12 haplotypes identified to be typed at high resolution. Typing of the HLA-A, B, C, DRB1/3/4/5, DQA/B1 and DPB1 genes was completed on all 99 donors. During the next period donors representing the 7/8 mismatch haplotypes will be invited to participate in the Antigen Recognition Site Allo-reactivity Assessment Project. Samples will be drawn, processed, and shipped for inclusion in in-vitro functional cellular assays

The high resolution HLA data generated through the project are routinely incorporated into all outcomes analyses performed by the NMDP/CIBMTR to provide the best HLA typing and matching information possible. The project has developed the largest fully validated pool of unrelated stem cell transplant donor-recipient HLA data in the world and is an unparalleled resource for transplant research. The data generated through the project have had a major impact on the evolution of the NMDP HLA matching requirements.

II.C. Immunogenetic Studies – Hypothesis 2:

Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.

Aim C.2.1: Analysis of non-HLA loci

Recent research has heightened interest in additional genetic polymorphisms which may modify the outcomes of transplantation. HLA genes other than the major histocompatibility complex (MHC) found on chromosome 6 and non-HLA genetic factors may all influence the suitability and success of allogeneic stem cell transplants. The largest body of data with clear correlation to unrelated stem cell transplant outcome was surrounding the role of Natural Killer (NK) cells. These cells express inhibitory receptors (KIR) that specifically interact with MHC class I molecules. Genes encoding for these Ig-like ligands are found on chromosome 19. The regulatory mechanism mediated by these receptors is thought to protect normal cells from autologous NK attack, while rendering cells for which class I expression is compromised (e.g. by tumor transformation or viral infection) or incompatible (e.g. by stem cell transplant) susceptible to NK-mediated killing. This has been shown to be responsible for anti-leukemic effects and protection against GVHD following allogeneic HSC transplantation.

Based on this information, the NMDP developed a pilot study to perform KIR ligand typing utilizing selected donor and recipient pair samples. The project was launched in early 2005 with ongoing support provided through the project period. The NMDP selected three laboratories to participate in the project through a competitive bid process. The primary objectives of the study were to:

- Move technology forward from the current practice of locus level typing to high resolution typing
- Disseminate information and protocols in an open source mechanism
- Develop reference lines for use in individual laboratories. Additionally, the project will provide more fully characterized and highly quality controlled transplant pairs for use in research studies connecting these factors to clinical outcome data

During the previous period, the KIR Typing Pilot Project completed the final typing on 435 Caucasian donor samples for 14 KIR genes (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1). However, the study encountered a high degree of genetic polymorphism and allelic ambiguity in the KIR loci. During this period all 91 remaining discrepancies were resolved and 128 potential new KIR alleles were re-analyzed. Seventy-eight samples were re-typed with 46 novel alleles described and submitted to the WHO nomenclature committee for registration and naming. In addition, presence/absence genotyping of the KIR loci was incorporated into the retrospective Donor/Recipient (D/R) Pair HLA typing project (II.C.1). To date 1173 pairs from the

Donor/Recipient pair's project have been typed for presence/absence of 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1).

The 435 donor samples from the KIR Typing Pilot Project represent the largest cohort of fully allele-level KIR typed samples to date and are a data rich reference resource for the KIR testing community. Project funds were used to produce and expand B-cell lymphoblastoid cell lines to provide reference material for the research community. Cell lines of common haplotypes and novel haplotypes, i.e. containing novel alleles, were produced. A panel of 58 cell lines was selected that represent 80% of the known KIR alleles as of KIR IPD database 2.1. These cell lines have been made available through the NMDP Research Repository for use by other investigators.

The results of the KIR Typing Pilot Project were presented as an abstract entitled, "Discerning KIR Haplotypes" at the 2008 ASHI annual meeting and received the ASHI Scholar Award.[10] The analysis included an update on KIR gene-content haplotype estimation from a donor population as well as the first-ever results of large-scale KIR allele level haplotype analysis. Further analysis of haplotype and linkage disequilibrium predictions were completed and presented at the 2009 KIR Polymorphism Workshop.[11] Also, the availability of reference cell lines and data were promoted to external researchers. A meeting was held at the NMDP to plan the development of a manuscript on the project findings and submission for publication is anticipated in the next year. The clinical correlation of KIR alleles with HCT outcome was initiated in collaboration with the International Histocompatibility Working Group – HCT component and analyses are ongoing.

NK cells have also been implicated in unrelated hematopoietic stem cell (HSC) transplant outcome through suppression of graft versus host disease, promotion of HSC engraftment, and mediation of graft versus leukemia effects. NK-HLA interaction through inhibitory KIR has been a major focus of investigations regarding the role of NK in HSC Transplantation.

During this grant period, development of the IPR (Immunobiology Project Results) database and application continued. This database will replace the existing HLA donor/recipient pairs database and has the capacity to process KIR, SNPs, or any other Immunobiological test results. Input file (HML) processing has been developed and the analysis of processing rules (lab-to-lab comparison, ambiguity analysis, data audits) is nearing completion. The development delivered the IPR database in time for sample group twenty-one (SG21) (which includes both HLA and KIR typing for research).

For SG21, it will mirror HLA processing in the current system and incorporate KIR processing (which is not available in the current system). Specific accomplishments included:

- The Scientific Services and Bioinformatics departments continued to collaborate on the design and development of the IPR database application and tools to support immunogenetic testing projects

- Work was done on implementing the acceptance, validation, storage of incoming data via HML. The next phase will develop and test the extension of the process to genotype lists (of immediate importance for KIR data) and the reporting of the whole process.
- Work was also done on implementing a web-browser-based application which will allow users to view typing results as stored in the database.
- Analysis of processing rules (lab-to-lab comparison, ambiguity analysis, data audits) has been put on hold until data-loading development is completed.
- Specifications are being written to transfer data from the old system to IPR.
- Work continued on a prototype project to recreate informational data stores.

Immunobiological test results generated through NMDP/CIBMTR approved studies and reported to the NMDP are summarized in Table 7. These data will be used for testing, validation and population of the IPR database.

Table 7: Immunobiology typing projects utilizing NMDP samples and contributing data to the IPR database

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
NK Cells, Their Receptors and Unrelated Donor Transplant	J. Miller	2300 pairs	KIR	RT-PCR, FACS, SSO, MALDI-TOF	Yes
Survey of Diversity of Immune Response Genes in Unrelated Hematopoietic Stem Cell Transplantation	C. Hurley	40 Pairs	cytokine and KIR	SBT	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Candidate Gene Study to Examine the Impact of Chemokine and Chemokine Receptor Gene Polymorphisms on the Incidence and Severity of Acute and Chronic GVHD	R. Abdi	1300 pairs	CCL1, CCL2, CCR5, CCR2, CX3CR1	Taqman PCR	Yes
Functional Significance of Killer Ig-like Receptor (KIR) Genes in HLA Matched and Mismatched Unrelated HCT	B. Dupont, K. Hsu	2000 pairs	KIR	SSP	Yes
Functional Significance of Cytokine Gene Polymorphism in Modulation Risk of Post-Transplant Complications	E. Petersdorf	2500 pairs	>30 Immune response genes	Taqman PCR	Yes
Identification of Functional SNPs in Unrelated HCT	E. Petersdorf	3500 pairs	Entire MHC region	Taqman PCR	In Process
Use of Female Donors with Pre-existing Antibody to H-Y Antigen will Result in Robust Serologic Response to H-Y Antigens in Male HSC transplantation Recipients	D. Miklos	288 pairs	H-Y Antigen	ELISA, protein array	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Multiplexed Genotyping of Human Minor Histocompatibility Antigens (mHAg): Clinical Relevance of mHAg Disparity in Stem Cell Transplantation	T. Ellis	730 pairs	mHAg	Allele-specific Primer Extension	Yes
Genetic Polymorphisms in the Genes Encoding Human Interleukin-7 Receptor-a: Prognostic significance in Allogeneic Stem Cell Transplantation	K. Muller	851 pairs	IL-7	Taqman PCR	Yes
The Effect of Non-Inherited Maternal Antigens in Cord Blood Transplantation	L. Baxter-Lowe	102 pairs	HLA	SBT	Yes
Detection of HLA Antibody in Single Antigen HLA-Mismatched Unrelated Donor Transplants	S. Arai, D. Miklos	200 pairs	Anti-body	ELISA, Protein array	Yes

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Stem Cell Transplantation and Their Relationship to Graft/Patient Outcome	R. Bray	111 pairs	Anti-bodies	Flow cytometry	Yes
Genome-wide Association in Unrelated Donor Transplant Recipients and Donors: A Pilot Study	R. Goyal	858 pairs	> 600,000 Genome wide SNPs	Human 610 - Quad V1 arrays	In process
SNPs in the p53 Pathway and Outcomes in URD HCT	B. DuPont	1500 pairs	p53, ATM, MDM2 and p21/Waf1	Taqman	In process
Association of Donor and Recipient Gene Polymorphisms of Drug and Innate Immune Response with Outcomes after URD HCT	V. Rocha	725 pairs	GSTP, GSTT, GSTM, UGT CD14, TIRAP, and NALPs	Taqman	In process
To Develop and Test a Prognostic Index for Survival in CML URD HCT	A. Dickinson	1100 pairs	TNF, IL-1RA and IL-10	Taqman	Yes
Evaluation of Lymphotoxin Alpha (LTA) Alleles in Relation to Relapse in AML	P. Posch	~600 samples	LTA	Taqman	In process

Study Title	Investigator	Number of Samples	Genes of interest	Testing Method	Data Submitted
Evaluation of TGF-beta-1 Promoter and Signal Peptide Polymorphisms as Risk Factors for Renal Dysfunction in HCT Patients Treated with Cyclosporine A	R. Shah	400 samples	TGF-beta-1	Taqman	Yes
Donor and Recipient Telomere Length as Predictors of Outcomes after Hematopoietic Stem Cell Transplant in Patients with Acquired Severe Aplastic Anemia	S. Gadalla	650 samples	Telomere length and Telomerase Polymorphisms	Taqman	In process
Development of a GVHD Prevention Biodiagnostic Test	R. Somogyi	450 samples	Gene Expression Array	Array	In process
Genetic polymorphisms and HCT related mortality Re: Pre-HCT conditioning in matched unrelated donor HCT	T. Hahn	>4,000 pairs	GWAS	Array	Pending funding

Aim C.2.2: Related Pairs Research Repository

The research affiliation between the NMDP and the IBMTR, executed in July 2004 to form the CIBMTR, provided a previously unavailable source of statistical and scientific expertise that can help ensure that existing repository resources are fully utilized. The CIBMTR offered an

unprecedented opportunity to expand the utility of the unrelated donor-recipient pair repository by including specimens from related pairs. Because of genetic identity for HLA haplotypes, related donor-recipient samples will greatly enhance the ability of researchers to conduct certain immunobiologic studies without the confounding effects of HLA disparity and will facilitate an organized approach to studying transplant biology across the full spectrum of allogeneic HSC transplantation.

Navy support for the operation of the Related Repository was no longer needed following the CIBMTR receipt of the HRSA contract to operate the SCTOD that included support for the related sample collection. Navy funds were reallocated to other programs with the exception of support for repository software enhancements. The repository software was updated to support the collection of related samples and sample collection began with a pilot project initiated at seven TCs following the release of FormsNet 2.0 in December 2007 for the collection of clinical outcome data under the SCTOD. At the end of the project period, 677 samples (317 donor/recipient pairs) had been submitted to the Repository.

During the project period, Scientific Services, Bioinformatics and IT staff continued development of the Research Sample Repository Tools suite to facilitate management of related, unrelated, and cord research samples. The tools suite includes the following modules:

- Vial Inventory Tool: used to view and search for available inventory
- Cell Culture Queue Management Tool: allows selection of low inventory samples for cell culture and inventory expansion
- Pick Management and Review Tool: facilitates the selection of samples and review/approval of sample shipments
- Customer Management Tool: tracks research sample customers by NMDP/CIBMTR project or study

The Vial Inventory and Customer Management tools were completed previously. The Pick Management and Review Tool were completed during the current project period. The Cell Culture Queue Management Tool requirements are complete and development was placed on hold due to the need for completion of the higher priority tools. The development of a publicly accessible inventory query tool was not completed. However, detailed tables describing the sample inventory were placed on the CIBMTR Website allowing the public a static view of the inventory.

Evaluation of Whole Genome Amplification (WGA) as a renewable source of DNA at the NMDP Research Repository

The NMDP Research Repository generates B-LCLs as a source of renewable DNA. The process is expensive and time intensive (12-16 weeks) with a success rate for recipient samples below 50%. Due to the high failure rate, the continued use of B-LCL could pose too high a risk of

complete loss of samples when only a single vial remains in inventory. WGA using commercially available validated kits is an alternative methodology for generating a renewable source of DNA on low inventory donor, cord, and recipient samples. The WGA process is time and labor efficient, effective on various sample types, and has a high success rate of amplifying, on average, 40ug of gDNA from 10ng starting material when high quality genomic DNA is used.

A pilot study was conducted to evaluate the effectiveness of the WGA assay on sample types stored in the Repository. The pilot involved the performance of WGA on varying sample types that were stored for varying lengths of time in the Repository followed by HLA- A, B, C, DRB1, DQB1, and DPB1 typing to validate the quality of the DNA. The sample types evaluated are listed in Table 8 below.

Table 8. Sample types evaluated for WGA

Sample Type	Range of Storage Dates	Storage Condition
PBMC	1989-1992	Liquid Nitrogen
PBMC	1998-2001	-80ºC
B-LCL	1994-1997	Liquid Nitrogen
B-LCL	1992-1993	-80ºC
Whole Blood	2003-2006	-80ºC
Whole Blood	2003-2006	Liquid Nitrogen
Granulocytes	1993-1994	-80ºC
Filter Paper	2003-2006	RT
Buccal Swabs	2007-2008	RT
Cord Blood – Filter paper	2007-2008	RT
Cord Blood - DNA	2002, 2005	-80ºC

Five individual samples of each sample type were distributed to a centralized laboratory for DNA extraction and WGA. All sample types yielded sufficient DNA to proceed with the WGA step (data not shown). The WGA assay used an input of 10ng of extracted DNA from each sample type and yielded a median 37-63ug of WGA product (Table 9).

Table 9. WGA product median yield and purity by sample type.

Sample Type	Median 260/280 Ratio	Median Yield (ug)
PBMC -80ºC	1.78	37.27
PBMC LN2	1.80	45.19
B-LCL -80ºC	1.74	59.71
B-LCL LN2	1.75	48.25
Whole Blood -80ºC	1.76	47.38
Whole Blood LN2	1.78	40.68
Granulocytes -80ºC	1.80	63.11
Filter Paper RT	1.72	41.79
Buccal Swabs RT	1.71	46.50
Cord Blood – Filter paper	1.72	43.38
Cord Blood - DNA	1.78	53.43

The WGA product was then transferred to a contract laboratory for HLA testing. The majority of the sample types produced problem free testing results that were fully concordant with the HLA typing of record. The laboratory did experience problems with filter paper and buccal swabs from unrelated donors. The extracted genomic DNA from both filter paper and buccal swabs was evaluated and found to be degraded. The WGA process may exacerbate the degradation leading to low molecular weight DNA that is problematic for HLA typing. The degradation led to substantial allele dropouts at HLA Class I and amplification failures for HLA-DPB1. Degradation problems were not observed for cord blood filter paper samples. However, one cord filter paper sample resulted in a different set of typing issues. The HLA-DRB1 had to be repeated twice and a silent mutation was found in exon 3 codon 95 (ATC>ATT) for HLA-A. The original typing strategy did not sequence this region, so it was unclear whether the point mutation was already present or introduced by the WGA procedure. The sample is currently under investigation to determine whether the silent mutation was present in the original sample or an artifact of the WGA process. The HLA typing issues are summarized in Table 10.

Table 10. HLA typing issues observed with WGA products from the varying sample types.

Sample Type	Weak Signals*	High Background*	Drop Out*	Total
PBMC -80ºC	0	6	0	6
PBMC LN2	4	0	0	4
B-LCL -80ºC	0	0	0	0
B-LCL LN2	1	2	0	3
Whole Blood -80ºC	0	3	0	3
Whole Blood LN2	1	6	0	7
Granulocytes -80ºC	1	7	0	8
Filter Paper RT	21	7	9	37
Buccal Swabs RT	12	9	10	31
Cord Blood – Filter paper	1	0	0	1
Cord Blood - DNA	0	0	0	0

WGA proved a promising alternative to B-LCL transformation to provide a renewable source of DNA for low volume samples in the Repository and is suitable for use on PBMC, granulocytes, whole blood, B-LCL, previously extracted DNA and non-degraded filter paper. The procedure is particularly valuable for the expansion of cord blood research samples due to the minute input requirements and will ensure that these extremely low volume precious samples are available for multiple studies. A proposal to transition from B-LCL transformation to WGA was presented to and approved by the NMDP Histocompatibility Advisory Group in July 2009.

II.D. Clinical Research in Transplantation – Hypothesis 1:

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Aim D.1.1: Observational Research, Clinical Trials and NIH Transplant Center

Cord Blood Research Activity

During the project period, the Cord Blood Research sub-Committee met monthly to discuss study priorities and plan analyses. The group completed development of educational sessions for presentation at the 2008 NMDP Council meeting including:

- A workshop entitled, "CFU Methodologies: Considerations in Practice Standards and Outcome Variability", that will cover issues related to the current CFU assay systems and new procedures designed to minimize interlab variability.
- A workshop entitled, "New Frontiers in Cord Blood Processing", that will provide an overview of cord blood processing methodologies and systems.
- A wet lab for cord blood bank technicians focused on best practices for CFU assay setup and enumeration.

Educational sessions were also developed for the 2009 NMDP Council meeting including:

- Cord Blood Transplants in Adults: A Growing Therapy: Session objectives are to review history of cord blood transplantation in adult patients, to discuss current practices in adult cord blood transplants, and to describe the role of cord blood in the future of adult stem cell transplantation.
- Strategies for Improving Outcomes in Cord Blood Transplant: Research and Practice: Session objectives are to review historical outcome data for cord blood transplant, to discuss the limitations of cord blood transplants, and to discuss innovation techniques that focus on improving cord blood transplant.

The subcommittee membership continued work on several ongoing pilot research projects. A subgroup developed a study focused on the evaluation of differential cellular recoveries for CBUs from various race groups with a focus on determining root causes of low cell yields from African American CBUs. MD Anderson Cancer Center, Duke, and the St. Louis Cord Blood Bank compiled the results of pre and post processing cell yields for CBUs from various racial/ethnic groups. Analysis of the results is ongoing.

The cell processing laboratory at Memorial Sloan-Kettering developed a modified gating strategy for CD34 viability assessment that correlates with engraftment potential in a single center study.[12] The subcommittee developed a feasibility study to evaluate and validate the gating procedure at other centers. A preliminary assessment of the archived flow cytometry files

at the MD Anderson Cancer Center laboratory revealed that the files could not be reanalyzed according to the MSKCC protocol. Therefore, the retrospective study was abandoned and the study placed on hold pending development of a prospective plan for assessment.

The Duke laboratory initiated a pilot project to evaluate various assay systems for CBU potency assessment prior to transplantation and found that expression of the enzyme aldehyde dehydrogenase (ALDH) was a reliable marker for stem cells. The preliminary results were presented at the HRSA advisory council meeting in December 2008. The subcommittee used the preliminary results to develop a multicenter study to extend the analysis and developed a grant entitled "Cord Blood Biomarkers for Engraftment", in response to RFA-OD-09-003. The study proposed to prospectively test CBU segments selected for confirmatory HLA testing through the NMDP for potency and then to correlate neutrophil engraftment in patients transplanted with these units with the potency assays. The primary hypothesis was that the ALDHbr dose, measured in a frozen segment from a banked CBU, would best correlate with engraftment after transplantation. If validated, it will provide a method to assay CBU potency before release of a unit to a transplant center. It will also result in selection of higher quality CB units for CBT. The grant was not awarded, however work began with project funds to validate the testing methodologies at the two centralized laboratories and the project will proceed in the project period

A study was developed to analyze the race and HLA matching of CBUs and recipients whose transplants were facilitated through the NMDP. The majority of CBUs distributed for racial minority recipients were not race matched. The results were presented as a poster at the 2009 ASHI annual meeting.[13] In brief, 1,990 consecutive NMDP distributed CBUs were evaluated for race and X/6 HLA match. The recipient population was restricted to self-reported race groups with sufficient numbers for evaluation: Asian (N=101), African American (AFA) (N=191), Hispanic (N=272), and White (N=1041). The recipient-CBU race match distribution is noted in Table 11 and the distribution based on HLA matching (6/6) in Table 12.

Table 11. Recipient CBU Race Match Distribution

	CBU Race				
Recipient Race	**Asian**	**AFA**	**Hispanic**	**White**	**Other**
Asian	39%	4%	6%	30%	22%
AFA	0%	41%	9%	29%	20%
Hispanic	<1%	4%	44%	32%	20%
White	1%	2%	7%	68%	22%

Table 12. Recipient CBU race match distribution for 6/6 HLA matches

Recipient Race	CBU Race				
	Asian	**AFA**	**Hispanic**	**White**	**Other**
Asian	67%	0%	0%	11%	22%
AFA	0%	20%	20%	40%	20%
Hispanic	0%	0%	65%	22%	13%
White	0%	0%	4%	73%	23%

The majority of CBUs distributed for racial minority recipients were not race matched (39-44%). However, the best HLA matching levels (6/6) were found in race matched pairs (65-73%), except AFA (20%). Recruitment strategies should continue to target a racially diverse population for the benefit of all racial groups.

A committee subgroup met at the 2009 ASH meeting to develop a CIBMTR protocol for a retrospective observational study of single versus double cord blood transplants in adult patients. The protocol was submitted to the CIBMTR Graft Sources Working Committee for review and will be presented during the BMT Tandem meeting next quarter.

The subcommittee was tasked by the NMDP Cord Blood Committee with the development of a white paper detailing recommendations/guidelines for the assessment of new assays (potency or other assays) relevant to cord blood banking and/or transplantation. A draft was developed and included the following chapters:

- Brief history of cord blood transplantation, with a focus on cord blood characteristics (ex. TNC) and recipient clinical indicators (ex. Degree of HLA match, diagnosis) that impact outcomes.
- A review of the key steps in CBU manufacturing (collection, processing, cryopreservation, storage) and handling (ex. transportation, short-term storage, thawing) that can impact unit potency
- A description of assays currently used to assess CBU quality
- Describe expectations for the next-generation of assays, including how the assays should be validated, implemented, and any regulatory implications

Resource for Clinical Investigations in Blood and Marrow Transplantation
During this grant, activities within the Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT) continued. The goal of this program is to provide an avenue for investigators to obtain statistical and data management support for Phase I and II prospective trials focusing on addressing various transplant issues. The following key elements were completed:

- Clinical Trials Advisory Committee (CTAC) met for its annual in person meeting during this grant period. This meeting occurred at the 2008 Tandem meetings. This committee has been charged with providing scientific review and recommendations on clinical trial proposals. The committee reviewed a total of 5 proposals of which two were approved to move forward to protocol developments and three denied. One of the approved proposals did not move to protocol development due to PI decision to not move forward with the study at this time.
- Managed all elements of the Adult Double Cord in patients with hematologic malignancies trial. Staff opened remaining sites, managed accrual, and performed site monitoring. At the end of this grant year, a total of 16 patients were accrued on this trial.
- Staff continued to provide support to the Blood and Marrow Transplant Clinical Trails Network (BMT CTN) PBSC vs Marrow Phase III trial. This support included managing the donor component of the study but also assisting the BMT CTN in the area of accrual initiatives on the recipient portion of the study. Activities included were:
    - Supported Donor Centers by providing continued training, tools, and updates
    - Performed monitoring activities at the donor centers
    - 328 donor/recipient pairs enrolled during this grant period.
- During this grant period, database development was completed for the Lenalidomide after allogeneic HCT for Myeloma trial. The trial was activated and accrual began. During this time, defects were identified and staff worked with the trial management system vendor to correct.

CIBMTR Observational Research

Support of the Observational Research program included statistical hours for managing studies within the Immunobiology (see section IID1.3 below), GVHD, and Graft Sources Working Committees. During this grant period staff performed proposal review, protocol development, data preparation, data analysis, and manuscript preparations. Details regarding the Immunobiology activities can be found in IID1.3 below. The GVHD and Graft Sources Working Committees published 4 manuscripts. During the grant period staff performed various other functions on over 20 other studies.

FormsNet Development

- FormsNet v2.5, v2.6, v2.6.1, and v2.6.2 were released during the year providing a number of bug fixes and enhancements including a major cleanup of forms tracking and internationalizations enhancements, imaging, and improved tracking for forms due.
- AGNIS has been released to production for forms 2900 and 2450 (death form and pre-TED). The data curation effort to register all 11,000 data elements in the caDSR has begun and is making steady progress with collaboration with a number of curators at the Minneapolis and Milwaukee campuses of CIBMTR and NCI.

Support for NIH Transplant Program
Funding from the Office of Naval Research provided the National Institute of Health the necessary resources to build a successful unrelated transplant program. NIH differs from other network members in that all patients are enrolled on a clinical trial for transplant. NIH performed unrelated transplants for 32 patients from January 1, 2008 through September 30, 2009 via seven open research protocols. Research protocols include unrelated transplants for acute hematologic malignancies, Mononuclear/Macrophage disease, congenital immune disorders and sickle cell disease. Research protocols also include studying approaches for dual cord blood transplants, targeted lymphocyte depletion and reduced intensity conditioning. Four new protocols are currently in development.

Aim D.1.2: Research with NMDP Donors

During this grant period staff continued activities in support of donor studies proposed by investigators outside the NMDP.

Dr. Galen Switzer's study to examine the impact race and culture has on a donor's decision to proceed through the confirmatory testing and donation process continued. Dr. Switzer has a five year NIH grant through the University of Pittsburgh to conduct the study.

Staff continued to collaborate on a COG KIR study. Activities included working with the donor center to ensure consent obtained, facilitating the collection of a donor blood sample, and shipment to the study lab. During the grant period a total of 67 donor samples were facilitated.

At the end of this grant period, staff members were involved in discussions with three investigators on how to provide the resources they may need for their research study.

Aim D.1.3: Expand Immunobiology Research

During the grant period funds were used to contract with an Immunogenetic Biostatistician at the Medical College of Wisconsin to provide support to NMDP Scientific Services and the CIBMTR Immunobiology working committee (IBWC). The biostatistician helped to conduct and direct research within the IBWC and assisted the Scientific Services department to advance models for registry composition analyses, haplotype frequencies, predictive algorithm, and automated donor selection algorithms.

To further stimulate completion of immunobiology studies within the CIBMTR, grant funds were used to provide monetary support to investigators whose studies require modest supplemental funding for completion. The IBWC awarded the following Immunobiology Research grants during the grant period:

- Support for a prospective research sample collection protocol for a study of cGVHD in long-term surviving male recipients who received HSCT from female donors.

- Support of sample costs for the expansion of an existing IBWC study investigating the role of mutations in the P53 gene pathway implicated in long-term survival after HCT. The initial results were presented at the 2008 ASH meeting.[14]
- Support for DNA extraction and preparation of 408 samples for a study evaluating genome wide genetic diversity and the impact on acute graft versus host disease.

The grant funds also supported significant outreach efforts by the IBWC leadership to increase exposure for the IBWC to basic scientists and other investigators. The IBWC leadership updated the committee brochure and informational materials for distribution at basic science meetings and had a presence at the annual ASH, BMT Tandem, EBMT, EFI, and ASHI meetings. The IBWC scientific director also delivered a plenary session talk on the impact of donor directed anti-HLA allo-antibodies in HLA mismatched stem cell transplantation at the 2009 Cord Blood Symposium in Los Angeles, California. The scientific director and Ph.D. statistician also attended an NIH sponsored workshop on clinical trials endpoints for acute graft versus host disease after allogeneic stem cell transplantation and participated in the CIBMTR External Scientific Agenda review.

In addition, the IBWC continued work on the 36 active studies in the committee, accepted seven new proposals for analysis, presented 8 abstracts, and submitted 7 manuscripts. Scientific activities included support for development of several ARRA challenge, U01, R01 and U54 grants in support of ongoing studies.

IBWC abstracts:

- Five abstracts were presented at the 2009 Tandem BMT meetings.[15-19]
- Three abstracts were presented at the 2009 EBMT meeting.[20-22]

IBWC Publications:

- Two manuscripts were accepted for publication.[23-24]

- Five manuscripts were submitted for publication:
    - David Valcarcel, et al. *One Antigen Mismatched Related vs. HLA-Matched Unrelated Donor Hematopoietic Transplantation in Adults with Acute Leukemia: CIBMTR Results in the Era of Molecular Typing.* Submitted to Blood.
    - Stephen Spellman, et al. *The Detection of Donor-Directed, HLA-Specific Alloantibodies in Recipients of Unrelated Hematopoietic Cell Transplantation is Predictive of Graft Failure.* Submitted to Blood.

- Susana Marino, et al. *Mismatched Unrelated Donor Stem Cell Transplantation: Identification of HLA Class I Amino Acid Substitutions Associated with Survival at Day 100*. Submitted to Blood.
- David McDermott, et al. *Donor and Recipient Chemokine Receptor CCR5 Genotype is Associated with Survival after Bone Marrow Transplantation.* Submitted to Blood.
- Yume Nguyen, et al. *Insufficient Evidence for Association of NOD2/CARD15 or Other Inflammatory Bowel Disease-Associated Markers on GVHD Incidence or Other Adverse Outcomes in T-Replete, Unrelated Donor Transplantation.* Submitted to Blood.

Attachment A –References

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Attachment B – Published Manuscripts and Abstracts Associated with this Grant

Manuscripts

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Abstracts

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